

Dynamical models of cortical circuits[☆]

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Cortical neurons operate within recurrent neuronal circuits. Dissecting their operation is key to understanding information processing in the cortex and requires transparent and adequate dynamical models of circuit function. Convergent evidence from experimental and theoretical studies indicates that strong feedback inhibition shapes the operating regime of cortical circuits. For circuits operating in inhibition-dominated regimes, mathematical and computational studies over the past several years achieved substantial advances in understanding response modulation and heterogeneity, emergent stimulus selectivity, inter-neuron correlations, and microstate dynamics. The latter indicate a surprisingly strong dependence of the collective circuit dynamics on the features of single neuron action potential generation. New approaches are needed to definitely characterize the cortical operating regime.

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Introduction

Cortical circuits are built of two main neuron classes — excitatory and inhibitory — that comprise about 80% and 20% of nerve cells respectively. An intricate network of synaptic connections links neurons within and across cortical layers. Long-ranging inputs drive and modulate activity in the local circuit, including afferent drive by

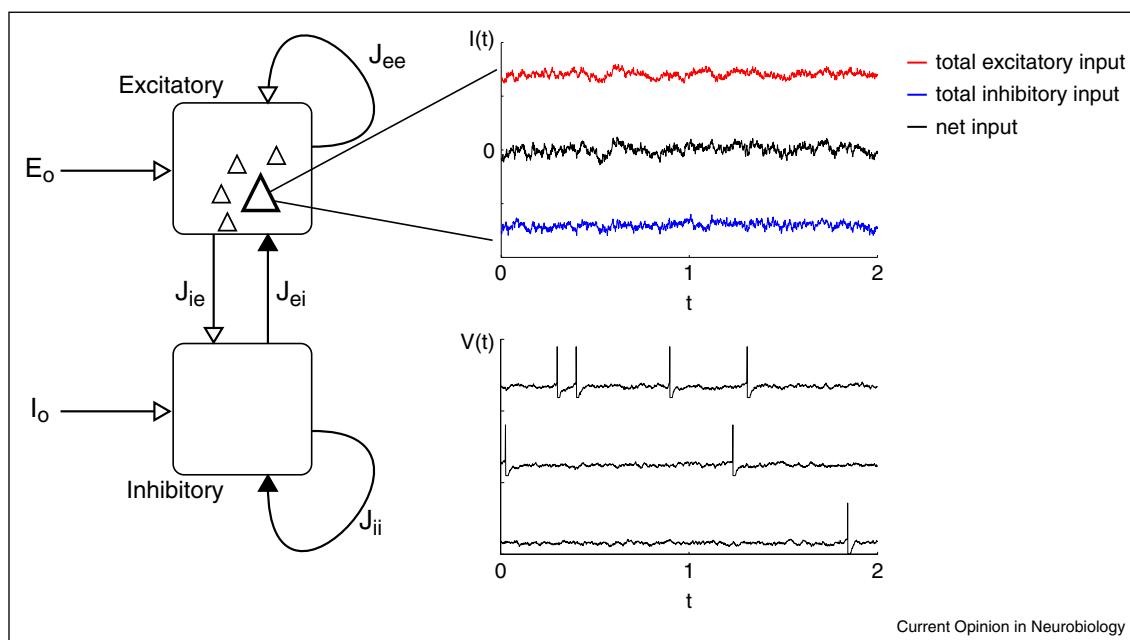
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specific thalamic nuclei and modulation by remote cortical cells [1,2]. Recurrent excitation in cortical circuits is believed to underlie the amplification of specific input patterns and the generation of persistent activity. In view of the large recurrently connected excitatory cell population, feedback inhibition appears indispensable for stabilizing recurrent cortical circuits. Recent functional and anatomical studies demonstrated that inhibitory connections in the local cortical circuit appear in general strong (see e.g. Ref. [3]) and dense [4–6]. This suggests that the inhibitory population as a whole can provide a dense ‘blanket of inhibition’ as a prerequisite for the utilization of recurrent excitation [7]. Over the past several years dynamical models of cortical circuits started to reveal unanticipated and counterintuitive roles of dominant feedback inhibition.

As any mathematically formalized model, models of cortical circuits have to strike a balance between idealization and detail. Current experimental approaches harnessing the ongoing progress in optophysiology, genetics and connectomics are beginning to picture cortical circuits in unprecedented detail. Substantial efforts in theoretical neuroscience are dedicated to laying the foundations for integrating and dissecting the emerging wealth of data. No amount of detail, however, can be expected to offset the need for idealization. Idealization — even counterfactual idealization, that is the neglect of known features — is required whenever the essential ingredients of a phenomenon need to be identified or when a qualitatively novel type of behavior demands conceptual advancement. For such challenges the ultimate aim is not realism but clarity, mathematical control, and the transparent penetration of complex phenomena. Recent work on the operating point of cortical circuits provides intriguing examples of paradoxical effects such as the suppression of activity by withdrawal of inhibition and excitation [8] or the emergence of response selectivity in random networks [9••]. The emerging understanding of such counterintuitive aspects of cortical operation promises to guide cortical circuit models to a mature balance of idealization and detail.

Balanced circuits, inhibition-stabilized networks (ISNs) and paradoxical responses

Dominant feedback inhibition plays a central role in virtually every dynamical model of cortical operation. Prime examples are models exhibiting *balanced states*, in which strong feed forward and recurrent excitation are balanced by equally strong recurrent and feedback

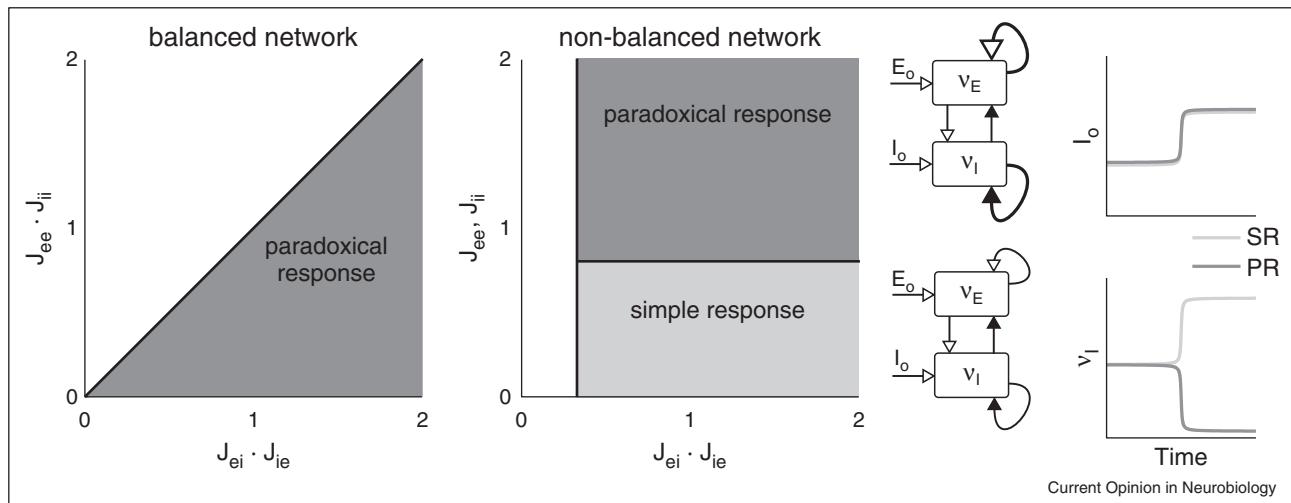
Figure 1

Balanced states robustly emerge in local circuits of inhibitory and excitatory neurons. Neurons in balanced networks are driven by residual input fluctuations that result from the near cancellation of excitatory and inhibitory inputs (upper right). The balance of excitatory and inhibitory inputs is a collective phenomenon and emerges from the recurrent interactions in the network. Balanced states were first found in sparse randomly connected networks. Recent work demonstrated the emergence of balanced states also in structured and more densely connected circuits and revealed that they actively suppress the occurrence of correlated activity. Cells in balanced networks robustly exhibit irregular and asynchronous activity patterns (lower left).

inhibition [10,11] (Fig. 1). Under such conditions spiking is driven by residual temporal fluctuations of net synaptic input and as a result is temporally irregular and only weakly correlated between cells. A related class of models are ISNs [8,12] (Fig. 2). ISNs are defined by recurrent excitation being so strong that runaway excitation cannot be prevented by any fixed amount of inhibition and stabilization can only be achieved if the activity of the inhibitory neuron population dynamically tracks every fluctuation in excitatory population activity. Balanced networks are in general ISNs but not all ISNs generate balanced states, strong input fluctuations and irregular asynchronous firing patterns. Above a threshold strength of recurrent excitation and inhibition, ISNs predict a paradoxical response to an additional external drive impinging on the inhibitory population (Fig. 2). One may naively expect that such a drive increases inhibition and reduces activity in the excitatory population by disynaptic inhibition. In a strongly coupled ISN, however, both activity levels drop leading to an effective ‘withdrawal’ of excitation and a paradoxical reduction of the level of feedback inhibition. Ozeki *et al.* recently found that this paradoxical response apparently underlies the phenomenon of surround suppression in cat V1 [8]. As the suppression of activity by a simultaneous reduction of excitation and inhibition in the local circuit seems hard to

explain in any other way, this phenomenon represents an intriguing piece of evidence for an inhibition stabilized operating regime in which excitation and inhibition are strong and dynamically matched. While feedback inhibition also appears strong in rodent sensory cortex, a recent study reported evidence for the simpler scenario of increased inhibition as the basis of surround suppression in mouse visual cortex [13]. Furthermore optogenetic activation of interneurons in mouse visual cortex can generate a wide variety of effects but so far has not provided evidence for paradoxical responses [14,15]. Further work is needed to clarify the phenomenology and determine whether similar or distinct mechanisms mediate surround suppression in rodent, carnivore and primate visual cortex.

Independent lines of experimental and theoretical evidence further support a cortical operating regime of strong feedback inhibition and recurrent excitation. Experimentally, London *et al.* found that inducing an additional spike in a single excitatory neuron in rodent barrel cortex can trigger a substantial rate response in the local circuit that indicates an intrinsically unstable level of recurrent excitation [16]. Intracellular studies of layer IV neurons in mouse visual and auditory cortex provide direct evidence for the recruitment of strong, amplifying

Figure 2

Inhibition-stabilized networks (ISNs) predict paradoxical responses beyond a threshold level of recurrent interactions. In ISNs recurrent excitation is so strong that runaway self-excitation can only be prevented if the inhibitory population tightly tracks fluctuations in the activity of the excitatory population. The schematic phase diagrams (left) indicate the occurrence of paradoxical responses in a section through the parameter space of a non-balanced and a balanced two population network, a special case of an ISN. The balanced network phase diagram also illustrates that parameter tuning is not required because balanced activity emerges from the network dynamics for an entire volume (grey) of parameter space. For strong recurrent interactions both the activity of the excitatory and the inhibitory population drop when the inhibitory population is subjected to an increased external drive (right, SR simple response, PR paradoxical response).

recurrent excitation [17–19] (discussed in Ref. [20]). In addition, theoretical studies that constructed comprehensive models for the contextual modulation of responses to grating stimuli in primate V1 ([21,22], see also Refs. [23,24]) are converging to a inhibition dominated local circuit structure. The same conclusion is supported by a study that tuned detailed recurrent circuit models to match the orientation tuning of subthreshold and spiking activity in pinwheel centers and orientation domains [25]. Finally, Persi *et al.* performed a comprehensive search for local circuit models that successfully reproduce contrast response functions in primate V1. They also conclude that cortical circuits without strong feedback inhibition are unable to match experimental observations [26].

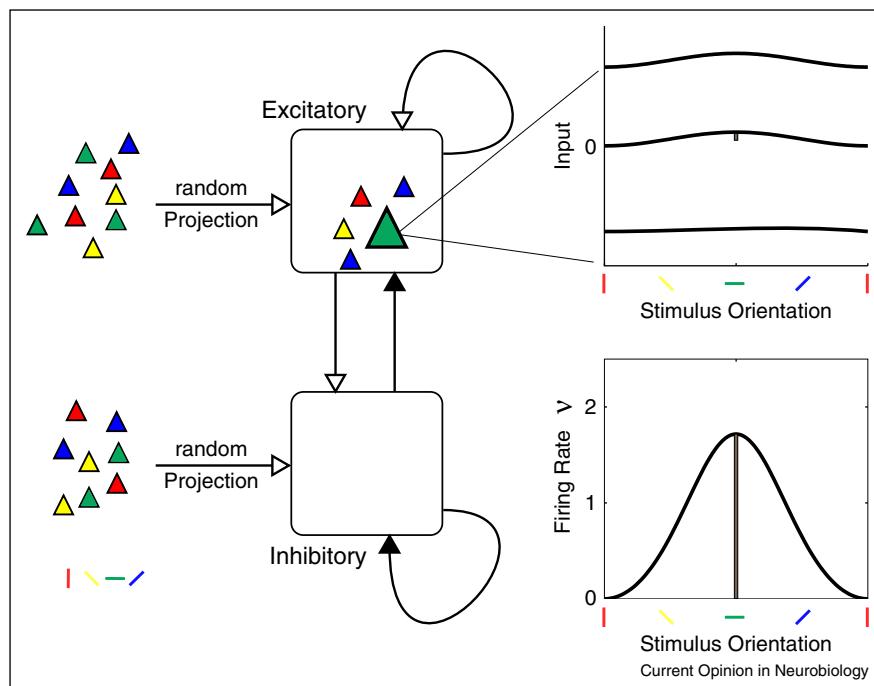
Do visual cortical circuits operate in a balanced state?

In an attempt to extend the study of ISNs toward defining the operating regime of V1 circuits, Ahmadian *et al.* recently studied networks of model neurons with expansive nonlinear input–output relations [27•]. These networks, called stabilized supralinear networks (SSNs), exhibit supralinear responses for weak inputs and sublinear and non-monotonic responses for strong inputs (see also Ref. [26]). This crossover from supralinear to sublinear responses promises a novel theoretical account for a wide range of normalization phenomena found in V1 [28]. Classical models of cortical circuits in the balanced state

are known to behave distinctly different. In these models, the condition of small average net input implies that the firing rates of the neuronal populations depend linearly on the external inputs. Ahmadian *et al.* therefore raised the question of whether the observed response non-linearity indicates that visual cortical networks are not operating in a balanced state. Two recent studies, however, show that response linearity is not a critical prediction of the balanced state [29•,30]. In these studies Mongillo, Hansel and coworkers for the first time presented a consistent treatment of balanced states in networks, in which synaptic inputs exhibit short-term plasticity such as synaptic depression and facilitation. Because of short-term plasticity the condition of small mean net input becomes nonlinear in the population firing rates and assumes a form that is similar to the equations that determine the firing rates in nonlinear rate models of the type used in [27•]. It is thus conceivable that a synaptic source of nonlinearity within a balanced network could result in similar normalization effects as predicted by a SSN. Further studies are needed to conclusively examine these alternative scenarios.

Feature selectivity and response heterogeneity in random circuits

Recently Hansel and van Vreeswijk showed that balanced states can lead to the emergence of sharp tuning for stimulus features even in randomly connected networks [9••]. They examined randomly wired networks of

Figure 3

Randomly connected networks in the balanced state driven by a random projection from a population of orientation-tuned neurons can generate highly selective responses. The total excitatory input to each neuron in the network is only weakly tuned. The balance of mean excitation and inhibition emerging in the network, however, largely cancels the untuned mean input. As a result, the neurons input output function can generate highly selective orientation tuning.

neurons receiving weakly orientation tuned net input as a result of random wiring. The emergent balance in the network, however, cancels the mean input and adjusts the population activity such that output firing is tuned as sharply as observed in V1 (Fig. 3). This study constitutes an important contribution towards understanding the operation of rodent visual cortex. In all rodents examined so far orientation selective V1 neurons are not organized into an orientation map but are arranged in an interspersed layout (reviewed in Refs. [1,31] see also Ref. [32]). Locally neurons are preferentially but not exclusively connected to neurons of similar orientation preference and receive inputs from cells exhibiting the full complement of preferred orientations [33–35]. Thus mature mouse V1 can be viewed as composed of intermingled subcircuits that are partially but not completely segregated (reviewed in Ref. [1]). So mouse V1 is certainly not per se a random network. It remains, however, an open question whether or not the observed specificity contributes to response selectivity. Interestingly, mature-like oriented receptive fields are observed already at eye opening when the preferential connectivity is not yet established [36]. This is consistent with the finding of Hansel and van Vreeswijk that the specific connectivity is not a necessary prerequisite

for the sharp orientation tuning. It is an important open question which neuronal operations are generated or enhanced by the selective excitatory connectivity in mouse visual cortex.

Balanced circuit models typically exhibit highly heterogeneous response properties that result from random variations in connectivity across neurons [10,11,37]. For instance, the balanced model for orientation tuning in rodent V1 [9**] exhibits substantial heterogeneity in orientation selectivity that is similar to the biologically observed heterogeneity in mouse visual cortex [38]. Balanced network models also robustly predict the most elementary kind of response heterogeneity: firing rate heterogeneity. Firing rate distributions have been examined in various cortical areas and appear to be generally broad and skewed toward low firing rates (reviewed in Ref. [39]). Roxin *et al.* recently presented a systematic analysis of firing rate distributions in balanced networks of neurons with expansive input-output relationships. Under a wide range of conditions these networks were found to robustly predict realistically broad firing rate distributions [40]. A slightly more complicated analysis can be performed to characterize the distribution of orientation selectivity in balanced

circuit models [37]. Such analyses will facilitate the quantitative comparison of balanced circuit predictions and population measurements. While the experimentally observed degree of response heterogeneity is consistent with generic predictions of balanced state models, biological response heterogeneity can in principle result from a wide range of sources. Dissecting the predicted response heterogeneity systematically should uncover more specific signatures of the distinct mechanisms.

Correlations and network structure

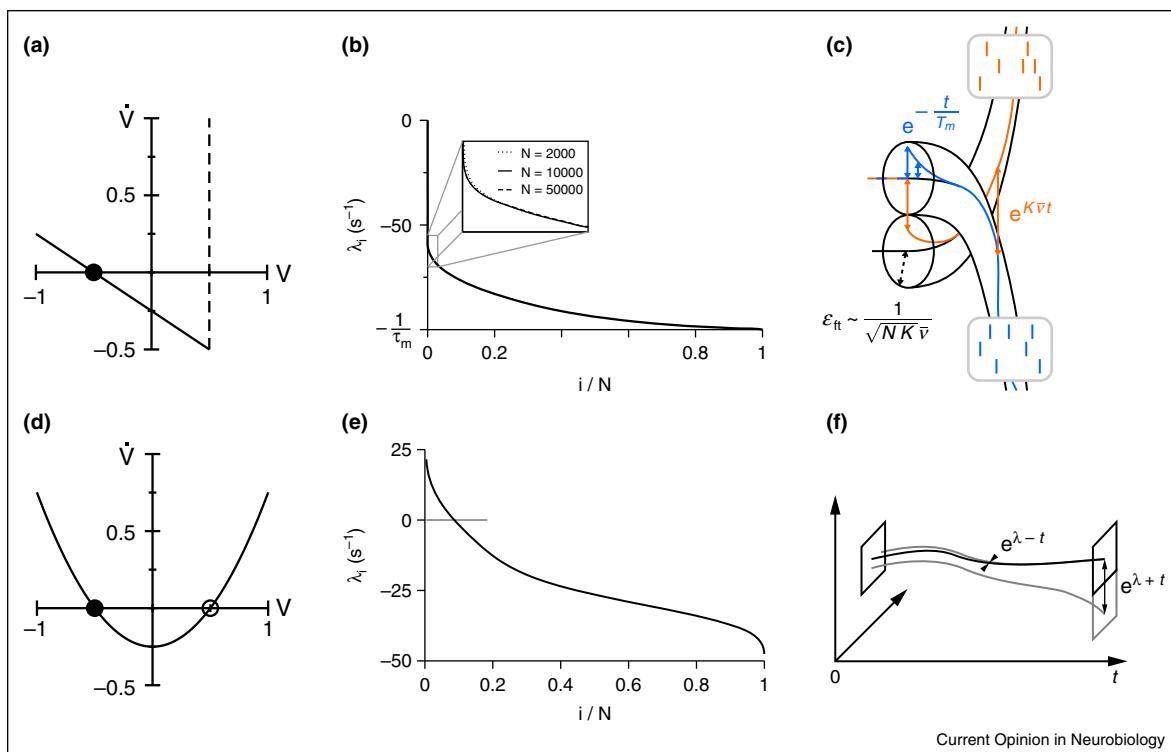
Correlations between the activities of different cortical neurons in a local circuit are on average relatively weak with correlation coefficients of 0.1 and below [41,42]. The classical models of balanced state networks are based on sparse random graphs in which the number of neurons in a population is much larger than the average number of synapses which is itself a large number. Numerical studies of balanced networks of spiking neurons, however, have for a long time indicated that a very sparse connectivity is not a strict requirement for the emergence of weakly correlated asynchronous states. Renart *et al.* recently extended the theoretical treatment of balanced networks to the case of dense connectivity, in which the number of connections per neuron scales proportional to the number of neurons in the population [43^{••}]. They showed that even with dense connectivity correlations are weak and vanish in the large network limit. The basis for this robust suppression of interneuron correlations is the capability of the inhibitory and excitatory inputs to not only cancel on average but also to track each other dynamically, canceling a substantial fraction of common input fluctuations [43^{••},44]. This feature seems to be a general property of balanced circuit models but so far has been analytically derived only for idealized networks of binary neurons [43^{••}].

Refined concepts for analyzing network generated patterns of correlations in spiking neuron networks have emerged over the past years. The transmission of input correlations into spike output correlations has been characterized for a diverse set of model neurons clarifying the dependence of correlation transmission on parameters of background input fluctuations, spike generation and synaptic characteristics [45–51]. Simple threshold neuron models apparently mimic correlation transmission in cortical neurons surprisingly well [48]. Using these approaches recent studies have started to dissect self-consistent patterns of inter-neuron spike correlations in networks with random and structured connectivity [52–55]. These studies are building a coherent mathematical foundation for future analyses on how single neuron and synaptic dynamics together with the circuit's connectome shape the structure and strength of emergent correlations. Notably, they generally presuppose that the emergent states are statistically stationary. Litwin-Kumar and Doiron, however, discovered that introducing clustering

motifs into balanced networks can lead to the emergence of slow firing rate fluctuations that deviate from a stationary process [56[•]]. It is thus an important open question how ubiquitous this phenomenon is and how structured or random a network needs to be to spontaneously generate slow rate fluctuations [72].

Chaotic dynamics, temporal-decorrelation and the bandwidth of neural population responses

Neuronal circuit models in the balanced state are non-linear high dimensional dynamical systems. They are thus expected to evolve chaotically in time. The first balanced circuit models in fact exhibited an extremely strong form of chaotic dynamics in which trajectories starting from similar initial conditions diverged faster than exponential [11]. Recent analyses of balanced circuits of spiking neuron models have revealed that the strength and nature of deterministic chaos can qualitatively depend on the choice of single neuron model [57,58,59,60^{••},61^{••}]. Balanced networks in which recurrent inhibition balances an external drive exhibit temporally irregular asynchronous spiking patterns. The generated sequences of spikes and subthreshold voltage fluctuations, however, can nevertheless be dynamically stable such that the network returns to a unique and invariant voltage trajectory and spike sequence after small perturbations [57,58,59,61^{••}] (Fig. 4). This stable irregular spiking dynamics was first found in purely inhibitory networks of pulse-coupled leaky integrate-and-fire neurons (LIF), but appears to persist when synaptic currents decay sufficiently fast and when some amount of recurrent excitation is included [58,59]. By contrast, balanced networks of exactly the same structure but composed of units that explicitly model the process of spike initiation exhibit irregular asynchronous activity with chaotic dynamics such that perturbed trajectories exponentially separate [60^{••},62]. The single neuron instability underlying spike initiation that is neglected in simple threshold neurons such as the LIF can apparently substantially contribute to the divergence of network state trajectories. These advances in the microscopic characterization of spiking network dynamics have started to provide new avenues for an information theoretical characterization of the repertoire of activity patterns that large spiking circuits generate. Monteforte and Wolf, for instance, were able to calculate the total entropy of distinct spike sequences that a balanced random network of LIF neurons can generate from a characterization of the network's phase space [61^{••}]. Studies of temporally driven balanced circuits (such as Refs. [62,63,73]) are needed to clarify the relationship of different types of chaotic dynamics and the representation of sensory information in patterns of network activity. Studies of network phase space organization have so far been performed mostly in networks of simple pulse coupled neurons. There are, however, no rigid limitations to generalizing

Figure 4

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The nature of collective chaos in balanced networks is sensitive to single neuron dynamics. The left panels represent the single neuron membrane potential dynamics of the leaky integrate-and-fire neuron (a) and the quadratic integrate-and-fire neuron (d). The middle panels show spectra of Lyapunov exponents (LEs) that characterize the divergence/convergence of state trajectories in the phase space of otherwise identical balanced networks of these model neurons (b,e). Positive LEs demonstrate a chaotic dynamics in which trajectories exponentially diverge. Negative LEs characterize the decay of perturbations in particular directions in phase space as indicated in the lower right scheme (f). In the LIF network all LEs are negative demonstrating that the irregular firing sequences generated by the network are stable. The upper right scheme (c) summarizes the geometrical properties of the basins of attraction of the different stable irregular firing sequences exhibited by the network. N is the number of neurons in the network, and K is the mean number of synaptic connections (modified from refs. 60,61).

the concepts and computational approaches to networks composed of more complex neuron models as long as they allow for an exact integration of the single neuron model between spike events.

A high speed of signal propagation is one basic advantage of asynchronous network states. In a large, asynchronously firing neuronal population a subset of cells is always close to threshold and thus ready to convey information rapidly. In balanced networks the speed of population responses is further increased by the strong net synaptic interactions [10,11]. Balanced networks are thus capable of rapid population responses even if the constituent neurons exhibit pronounced low pass characteristics. Recent experimental studies have started to address the bandwidth of spike encoding in fluctuation driven populations of real cortical neurons [64–68]. These studies consistently report that population responses are surprisingly rapid even in the absence of recurrent interactions. Even in response to very weak stimuli, populations of pyramidal cells can change their firing rate

within less than a millisecond — at least an order of magnitude faster than expected from their membrane time constant [67]. Such rapid responses to weak stimuli have been theoretically predicted for simplified neuron models such as the leaky integrate-and-fire neuron, but seemed to be absent in biophysically more realistic models (see discussion in Ref. [67]). The biophysical basis of the high bandwidth of neural population encoding in the fluctuation driven regime is currently not understood and calls for a reinvestigation of the basic processes of action potential generation [69–71]. Further theoretical work is needed to disentangle the relative contributions of strong recurrent interactions and single neuron bandwidth to the processing speed of cortical circuits.

Conclusions

Many lines of current evidence indicate an inhibition dominated operating regime of cortical circuits in which recurrent excitation and feedback inhibition are strong and dynamically matched. Counter-intuitive theoretical

predictions such as the paradoxical response of ISNs [8,12] or the emergence of orientation selectivity from balanced random networks [9••] are contributing to our understanding cortical circuit operation. Theoretical studies over the past several years have strongly expanded the toolbox for a mathematically accurate and controlled dissection of cortical circuit models in balanced and inhibition-dominated network states. Together with the current development of powerful new approaches for the experimental interrogation of cortical networks this progress provides a strong basis for discerning the mode of operation of cortical networks with a balance of theory and experiment.

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