# From working memory to epilepsy: Dynamics of facilitation and inhibition in a cortical network

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Persistent states are believed to be the correlate for short-term or working memory. Using a previously derived model for working memory, we show that disruption of the lateral inhibition can lead to a variety of pathological states. These states are analogs of reflex or pattern-sensitive epilepsy. Simulations, numerical bifurcation analysis, and fast-slow decomposition are used to explore the dynamics of this network. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3080663]

**The ability to maintain information in short-term memory for manipulation and use in subsequent action underlies virtually every aspect of cognitive function. This ability, referred to as working memory, is believed to arise through persistent states present in recurrent nonlinear neural networks in the cerebral cortex. There are a number of pathologies thought to be related to the disruption of the normal circuitry in the cortex. Among these is reflex or pattern-sensitive epilepsy, a type of seizure which is generated with very specific sensory stimuli. We suggest that changes in negative feedback in a working memory circuit are sufficient to explain the dynamics of reflex epilepsy.**

## I. INTRODUCTION

While the mechanisms of working memory are unknown, typically in most models these states correspond to stable attractors and dynamics arising in those recurrent networks (Amit, 1989, 1995; Amit and Tsodyks, 1991a, 1991b; Amit and Brunel, 1997a, 1997b; Wang, 1999; Bruenel and Wang, 2001; Compte *et al.*, 2000; Dursteewitz *et al.*, 2000). It is assumed that derangement of these ubiquitous recurrent cortical networks plays a fundamental role in various neuropatholgies. Particularly, it has long been recognized that recurrent impulses are a critical factor in generating hyperexcitability and recruitment which are the essential features characterizing seizures and epilepsies (Johnston and Brown, 1981; Traub and Wong, 1982; Lee and Hablitz, 1989; Traub and Miles, 1991; Traub *et al.*, 1993). Epileptic seizures represent temporary episodic periods of increased network excitation with variable propagation. It is suggestive to assume that the type of pathological activity observed in seizures/epilepsies is a function of inherent dynamics of recurrent working memory networks. Working memory has provided the archetype of persistently active states. Neuronal working memory networks remain active after the presentation of a cue (memorandum) during a delay period (Funahashi *et al.*, 1989, Fuster and Alexander, 1971). These persistent states may be maintained through a relative balance of excitation and inhibition (Shu *et al.*, 2003; Haider *et al.*, 2006) or through asynchrony and terminated through synchronization (Gutkin *et al.*, 2001). Numerous studies have demonstrated deficits in working memory function in epileptic subjects (Grippo *et al.*, 1996; Cowey and Green, 1996; Abrahams *et al.*, 1999; Koepp, 2005; Treitz *et al.*, to be published).

With the exception of neurological disorders due to malnutrition, epilepsy is the most prominent disorder in the world effecting approximately 1% of the population. It is estimated that there is a 10% lifetime risk of exhibiting a single seizure, approximately one-third of which will develop epilepsy. Epilepsy/seizures can arise in a number of varied forms, with potentially similar or varied underlying mechanisms. While epileptic seizures involve paroxysmal bursting of neurons in a local circuit, the clinical manifestations of seizures result mostly from spread of activity from local circuits to involve adjacent and remote brain regions. While in working memory, widespread populations are activated in normal cognitive function, and perhaps are related to binding, in seizure activity the recruitment of cortical networks and populations occur in a nondiscriminant pathological fashion. How different brain regions or populations are recruited is not well understood, and it is not known how to stop ongoing seizure propagation or prevent seizure activity. Further, little is known as to how seizures either begin or cease (Timofeev and Steriade, 2004). While it has been a long-standing belief that a connection between hyperactivity and hypersynchrony is fundamental in seizures, it has recently been shown that hypersynchrony is unnecessary to produce seizurelike bursting (Netoff and Schiff, 2002, Van Drongelen *et al.*, 2003). There is much evidence suggesting that seizures described as a straightforward increase in synchronization between neurons may be too simplistic. Computational and experimental models have shown, however, that low levels of excitatory coupling may be a prerequisite for some types of seizure onset (Pumain *et al.*, 1985, Feng and Durand, 2004; Van Drongelen *et al.*, 2005).

Synapses between neurons are known to undergo changes in their strength and dynamics. In working memory function, dynamic synapses (i.e., through synaptic facilitation) in recurrent networks can result in the normally observed persistent activation (Barak and Tsodyks, 2007; Verduzco-Flores *et al.*, unpublished). A reasonable postulate

 

widely proposed is that the development of epilepsy and seizures results from a shift in the balance between excitation and inhibition toward excitation (Dichter and Ayala, 1987; Galarreta and Hestrin 1998; Nelson and Turrigiano, 1998). Further a critical role is believed to be played by recurrent synaptic excitation in epileptogenesis (Johnston and Brown, 1981; Traub and Wong, 1982; Lee and Hablitz, 1989; Traub and Miles, 1991; Traub *et al.*, 1993). For example, synchronized bursting is favored by strong recurrent excitation between principal neurons and by disinhibition (review by Traub and Miles, 1991). It has been recognized increasingly that epileptic seizures are a dynamic disease caused by a change in the state of the brain dynamical system (Schiff, 1998). Different types of seizures have been viewed as bifurcations between distinct types of nonlinear dynamics (Wendling *et al.*, 2002). Nonlinear dynamics can advance our understanding (Larter *et al.*, 1999; Robinson *et al.*, 2002) of the spatial and temporal behaviors of seizures. Seizures may be triggered by some change in network parameters and/or inputs not evident to an observer (Lopes da Silva *et al.*, 2003). In the so-called reflex epilepsies, seizures are precipitated by some particular influx of afferent impulses and may be induced by a wide range of external stimuli of different modalities such as photic stimulation, geometric patterns, music, or computer video games (Tobimatsu *et al.*, 1999; Hayashi *et al.*, 1998), or internal cognitive processes, such as mathematical calculation. In a normal cortex, such external or internal stimuli might cause a transient, harmless modification of cortical activity, while in a predisposed brain they can induce massive synchronous discharges leading eventually to a seizure. It has been assumed that the stimulus leads to a dynamical change in the underlying attractor that facilitates the transition to the ictal phase (bifurcation). It has been proposed, for example, that in neuronal networks in the brain (Robinson *et al.*, 2002) the onset of seizures occurs via a transition from stable linear dynamics via linear instability to nonlinear behavior.

In humans, short electrical stimulation applied during cortical mappings is able to produce repetitive or periodic excitatory discharges in the cortex. In patients with epilepsy those discharges can progress to produce clinical seizures. However, in some cases a second electrical stimulation may stop those discharges. The fact that external electrical stimulation may terminate that activity in some cases raises the possibility of a method for seizure control. Uncertainties and variability in the ability of electrical stimulation to terminate the pathological discharge activity though imply that theoretical and model systems might be useful to understand the mechanism of action of these techniques. In contrast to the generation and termination of seizures via various invasive electrical stimulations, seizures may be generated and prevented or terminated through external stimulation. In particular, while stimulation with particular music is known to induce seizures in predisposed individuals, other music has been reported to prevent or terminate epileptiform activity (Hughes *et al.*, 1998; Shaw and Bodner, 2005; Turner, 2004a, 2004b; Bodner *et al.*, unpublished).

The potential modulation of termination seizure activity by brain stimulation is attracting considerable attention. Recently there has been growing interest in neural stimulation to reduce seizure frequency. Approaches include, for example, vagal nerve and thalamic stimulation and event-driven stimulation to terminate repetitive bursting. Modeling the effects of certain characteristics in the stimulation of working memory networks, such as specific spatiotemporal patterns, could yield efficient and minimally invasive approaches for treatment of epileptic patients. A related issue to initiation and/or termination of seizures is the mechanisms and dynamics by which a seizure recruits cortical areas and spreads within the cortex. Nonlinear dynamics can advance our understanding of the spatial and temporal behaviors of seizures (Larter *et al.*, 1999; Robinson *et al.*, 2002). Combining the concepts of neurphysiology of neural networks with the mathematics of nonlinear systems can help lead to an understanding of these mechanisms since neural networks are nonlinear systems with complex dynamics. This essential aspect must be accounted for in order to understand how neural network can have bistable memory states (or multistable states) and exhibit bifurcation between those states.

In this work we present a model of a working memory network and explore its nonlinear dynamic behavior in normal and seizure/epileptic states. Particularly we examine how the network can transition from normal working memory behavior dynamics to those characteristic of seizure activities particularly widespread recruitment of populations with varying degrees of synchronous oscillatory behavior. We propose that facilitation and inherent network parameters can bias neuronal activity to that of recruitment and seizure. We demonstrate that seizure behavior can be elicited in the model through input with specific temporal and/or spatial characteristics, simulating reflex epilepsies. Finally, we show that seizure activity may be also be terminated by input to the network with specific temporal characteristics. We start the paper by introducing a network of $N=20$ populations, each of which consists of three variables representing the activity of the excitatory and inhibitory neurons and the degree of facilitation of the excitatory synapses. We show the "normal" behavior for this network which consists of the selection and maintenance of a salient input. We then alter the strength of lateral excitatory to inhibitory connections to mimic pathology and find a variety of disruptive states. In order to better understand these, we study a two population model using bifurcation analysis. We find the attractors and then characterize the basins of attraction for each of the stable states by varying the frequency and strength of transient stimuli. We look at a single population and use the method of averaging to clarify why there are so many attractors. Finally, we explore possible mechanisms for the termination of seizures using the results from the previous sections.

## II. METHODS

We build on a previously defined model for working memory in a neural network based on the interactions between inhibitory and excitatory neurons as well as synaptic facilitation. The network involves coupling several modules each of which is a three-dimensional system of the form

$$\tau_u \frac{du}{dt} = -u + f(a_{ee}(1+kw)u - a_{ie}v - \theta_e + c_e p(t)), \quad (1)$$

$$\tau_v \frac{du}{dt} = -v + f(a_{ei}u - a_{ii}v - \theta_i + c_i p(t)), \quad (2)$$

$$\tau_w \frac{dw}{dt} = -w + f(\gamma(u-\theta_w))[w_{\max} - w]. \quad (3)$$

In this model, $u$ represents the firing rate of the population of excitatory neurons and $v$ the firing rate of the population of inhibitory neurons. The main nonlinearity is $f(x)=1/(1+\exp(-x))$. Coupling parameters $a_{jk}$ are all non-negative. $w$ represents a slow activity-dependent facilitation of the connection strength. That is, as $u$ fires enough above the threshold $\theta_w$, then $w$ slowly moves toward $w_{\max}$. The parameter $k$ characterizes the importance of the facilitation. The function $p(t)$ represents external input to the system.

The simplest network involves coupling a pair of these models. Coupling is allowed only through the excitatory cell. (As this pair represents a local cortical network, coupling between networks is mediated primarily through long excitatory connections which can project to either excitatory or inhibitory neurons.) Thus, the $u$ equation has a term of the form $d_{ee}(1+k\hat{w})\hat{u}$ added to the inside of the nonlinearity $f$, and the $v$ equation, a term of the form $d_{ei}\hat{u}$. In absence of the facilitation, the $(u,v)$—system is the classic Wilson–Cowan equation. Facilitation allows there to be a number of different coexistent stable states.

In much of the paper, we study the larger network of $N=20$ modules with coupling from the excitatory cells to other excitatory cells and to inhibitory cells. There is only facilitation of the excitatory-excitatory cells. For the one- and two-population models, we chose the following parameters: $a_{1ee}=12.3, a_{ie}=10.1, a_{ei}=11, a_{ii}=7$, $d_{ee}=0.7, d_{ei}=3.5$, $k=0.7$, $\theta_e=2.4, \theta_i=2.8, \theta_w=0.5$, $\gamma=5$, $w_{\max}=0.7$, and $\tau_u=0.02, \tau_v=0.04, \tau_w=2$. The stimulus has the form

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$$p(t) = \exp[-20(1-\cos(2\pi t/P_0))],$$

where $P_0$ is the period. (All time units are in seconds.) It is applied generally for 2–3 s and with varying strengths to the inhibitory and excitatory populations. For the networks consisting of 20 populations, all parameters are randomly varied between 2% and 5% around the above values.

## III. RESULTS

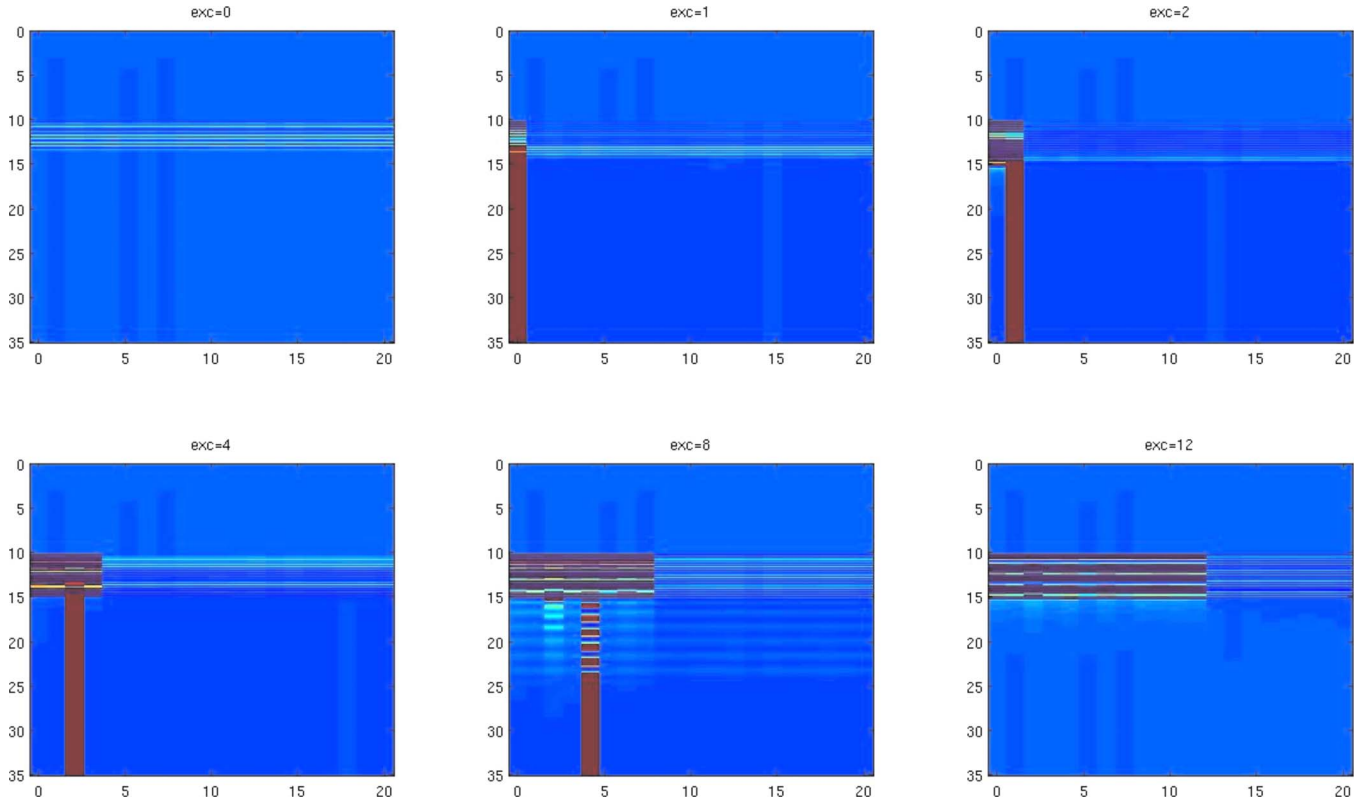
The idea of working memory is that a network can maintain a local area of sustained neural activity after a stimulus is removed. Almost all models of this phenomena involve selective bistability between a quiet resting state and a state of sustained activity. Essentially, if a specific stimulus arises, then the population of neurons that best responds to that stimulus will turn on and suppress other populations of neurons. Recurrent excitatory connections (and in our model, the synaptic facilitation) enable the stimulated population to stay on after the stimulus is removed so that the network can "remember" which population was stimulated. This kind of memory is also called short-term memory. In this and the ensuing parts of the paper, we want to show that (i) there can be temporal sensitivities to these networks and (ii) explore how damage to the inhibition (specifically the excitatory to inhibitory connections, $d_{ei}, a_{ei}$) can destroy the working memory properties in dynamically interesting and possibly clinically relevant means. To do this, we start with a network model and show a number of complex features as the network is "damaged" through the weakening of the $d_{ei}, a_{ei}$ connections. We then turn to a two population model and use numerical bifurcation theory to understand the various attractors. Then we use a single population and the method of averaging to explain some parts of the bifurcation diagram.

Our main assumption is that damage of the inhibition is responsible for the general phenomena of reflex epilepsy and that periodic stimuli are largely responsible for reflex epilepsies. Thus, in general, $p(t)$ will be a periodic stimulus with some narrow range of frequencies.

### A. Normal parameters

We have tuned our model in such a way that a single population can stay excited after a stimulus. This property is implemented by assuming broad excitatory to inhibitory coupling ($E$-$I$) and strong local inhibition $I$-$E$ in the network. Intuitively, if the population of excitatory cells is turned on, then that will also excite the inhibitory cells of other populations which will keep these populations suppressed. Since there are also excitatory to excitatory ($E$-$E$) connections and strong local $E$-$I$ connections, how is it possible to maintain activity in only one population? This is done through the slow facilitation. If a single population is strongly stimulated, then the facilitation for that population will build up and allow it to remain high once the stimulus is removed. The other populations which have not been directly stimulated will become excited but not sufficiently to remain permanently on, especially in light of the strong inhibition.

In each of the following simulations, a periodic stimulus is given with a particular frequency to all the populations in the network, and the first $k$ populations in the network are given a larger version of the same stimulus. The stimulus lasts for 5 s and the simulation lasts for 35 s. Figure 1 shows the behavior of the normal network which undergoes winner-take-all working memory behavior as long as the number of stimulated populations is sufficiently small. The first five panels ($k=0,1,2,4,8$) show that a single winner emerges when less than about half the network is stimulated. When only a single population is stimulated, that population will emerge as winner. However, when multiple populations are stimulated, the heterogeneity in the network (due to small random changes in the parameters) breaks the symmetry and a particular winner emerges (in this case population three). However, if more than about half the populations are stimulated (for example, 12/20), then the feedback inhibition is sufficient to prevent any population from emerging as the winner. Thus, the long-range recurrent inhibition acts to constrain the network in such a way as to prevent more than one stimulus to be selected.




AQ: #26 FIG. 1. (Color online) Behavior of the 20 population network with normal ($d_{ei}$=3.5) inhibition. All cells are given a mild background stimulus and the first $k$ cells are given a strong stimulus. Time (seconds) is indicated on the vertical axis and the population numbers are given on the horizontal axis. The excited populations are indicated above each graph. Blue indicates baseline firing rate, light blue indicates slightly higher than baseline firing rates, and red indicates activated (above baseline) firing.

## B. Pathology

### *1. All E-I disrupted*

Our main hypothesis is that reflex epilepsy is a consequence of the breakdown of feedback inhibition. There are several ways to disrupt inhibition: change the thresholds ($\theta_i$), the *E-I* connections ($d_{ei}$,$a_{ei}$) or the *I-E* connections ($a_{ie}$). In this paper, we alter *E-I* connections but manipulating *I-E* produces a similar effect (simulations not shown). Figure 2 shows that a strong reduction in the *E-I* connections (from 3.5 to 1.59) causes a loss of selectivity to the network. The resting background state remains stable to small enough perturbations, and if a single population is activated ($k$=1), then that memory can be maintained. However, if more than one population is excited, multiple populations maintain activity and selectivity is lost. An interesting transient in which populations begin to oscillate before settling to a steady state solution can be seen in several of the simulations.

Figure 3 shows what happens when the inhibition is not quite as reduced, (2/3.5 instead of 1.59/3.5). A distinctive frequency dependence on the stimulus emerges. Here all the populations are stimulated at three different frequencies leading to three different steady state behaviors. At 5 Hz (period is 0.2 s), the populations break into clusters which are separated by a half cycle. The number of clusters in each group can vary; an expanded view is shown in the lower panel. At a lower frequency of 3.3 Hz, synchronous oscillations emerge. Each population fires at the same frequency. Finally, at 2.5 Hz stimulus, there is again WTA behavior; however, the emerging patterns have nothing to do with the stimulus. AQ: #7

### *2. Partial disinhibition*

A more biologically likely scenario would be that only some local areas are pathological. That is, the disinhibition is "broken" for a finite number of populations. Figure 4 shows some simulations of the 20 population model when 1, 2, or 5 populations have reduced *E-I* connections. A single damaged population ($A$) allows for selective memory and competition as long as the damaged population is not among those stimulated. If it is stimulated, then it always is selected (compare the $A$, 1,2 versus 4). Panel (B) shows that background stimulation is enough to keep the damaged population active at all times after the stimulus, and this is sufficient to suppress any selectivity of more strongly excited populations. Indeed the simulation shows that the constant activity of the damaged population prevents the selection of the first or second populations when they are strongly activated. Figure 4(c) shows a similar result for damage to populations 4 and 5. Interestingly in this and also to some extent in 4$A$, the selected population does not go to a fixed point but rather oscillates. Finally, with five damaged populations, Fig. 4(d) shows that it can be difficult to get an undamaged population to stay activated due to the strong surround inhibition which comes from the higher activity of the damaged population. Because the damaged population has less inhibition, it is more active

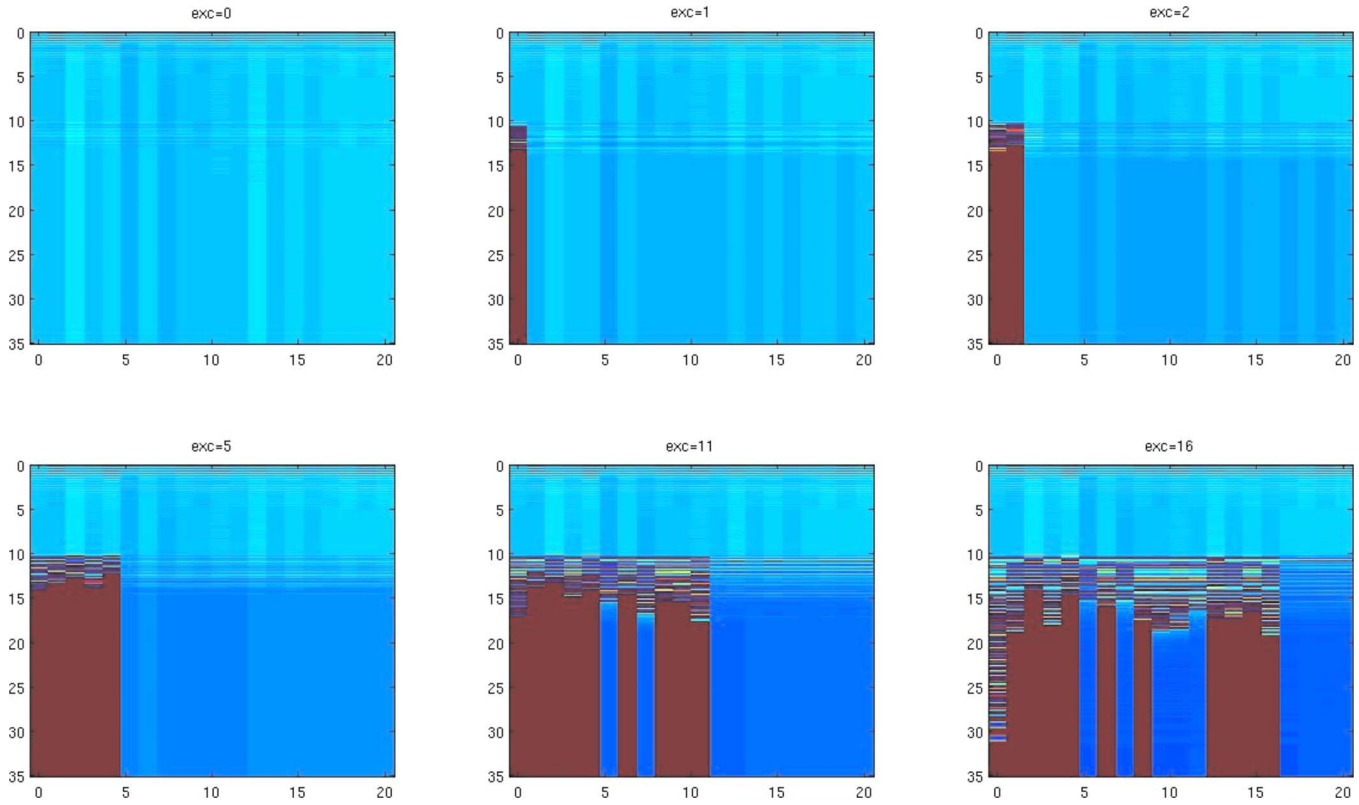



FIG. 2. (Color online) Behavior of the 20 population network with diminished ($d_{ei}$=1.59) inhibition. All cells are given a mild background stimulus and the first $k$ cells are given a strong stimulus.

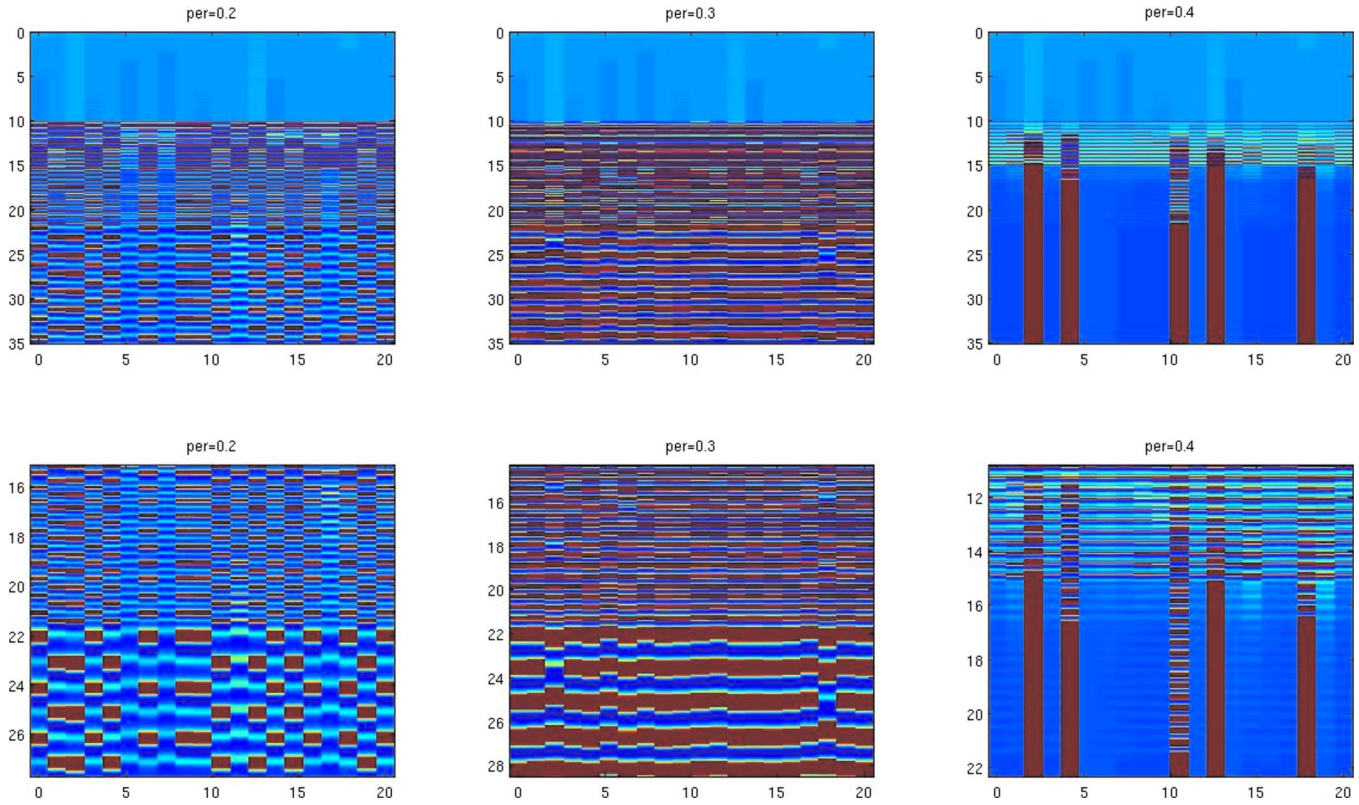



FIG. 3. (Color online) Behavior of the 20 population network with diminished ($d_{ei}$=2) inhibition. Here, all cells are stimulated with different periodic stimuli. Lower panels are an expanded view of upper panels.

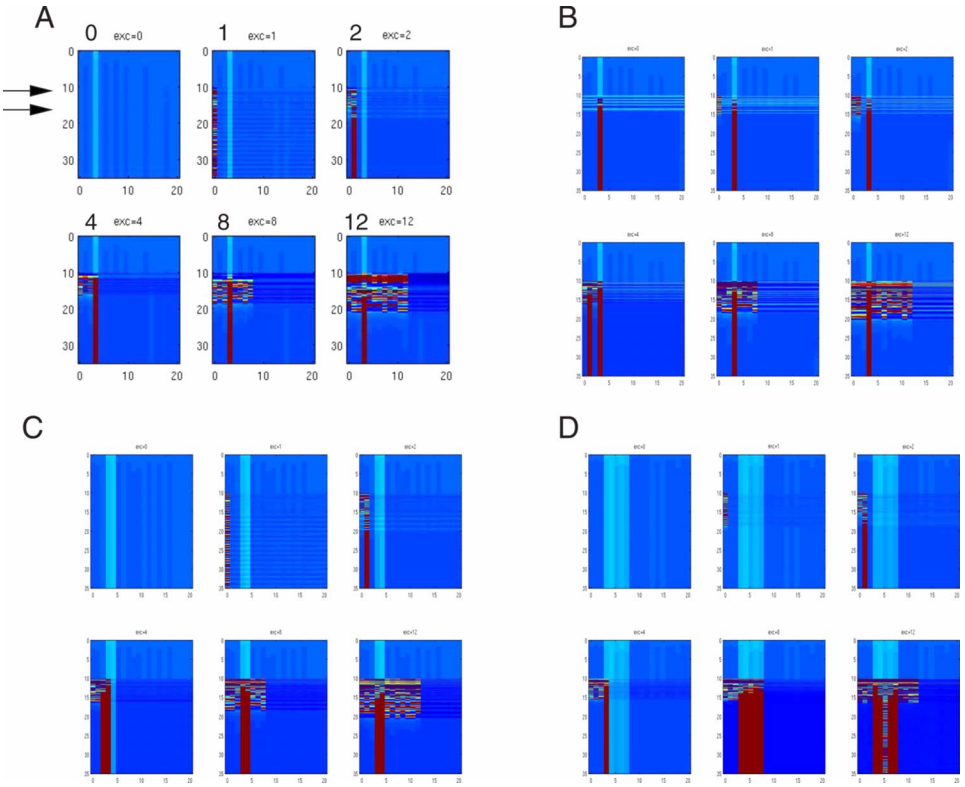



FIG. 4. (Color online) The effects of localized damage on the network. Each panel shows a simulation for 30 s after 5 s of stimulus (arrows) and the first $k$ populations ($k=0,1,2,4,8,12$). In panel B, in addition to local stimulation, there is also background stimulation. (a) Population 4 is damaged and once stimulated will always "win." (b) With background, the damaged population is always active even with weak (background) stimulation. (c) Similar to (a) but populations 4 and 5 are damaged and can both stay on when stimulated. (d) As in (a) and (c), but for five damaged populations.

and able to suppress the other populations, even though it is not highly activated (light blue rather than red).

## IV. TWO-POPULATION MODEL

In order to gain some insight into how damage reduces selectivity and produces a variety of pathological responses, we turn to a two-population model of identical groups and such that we reduce the cross inhibition. We first treat the *E-I* coupling as a parameter and find the attractors for the network using numerical bifurcation methods. Then we attempt to explain how stimuli affect a switch from rest to a specific attractor.

### A. Attractors

Figure 5 shows a sketch of the bifurcation diagram for the two-population model as a function of the parameter $d_{ei}$, which is the cross population *E-I* connection strength. We now describe the attractors and how they are connected and where they exist. We start on the dark blue curve at the asterisk and move to the left. This starting point represents a state in which both populations are at rest, in their low state. As the $d_{ei}$ decreases, there is a Hopf bifurcation (a) and this state loses stability. Thus, the network cannot remain quiescent below $d_a \approx 1.713$. As we continue along this unstable symmetric branch, there is a pitchfork bifurcation (b) which spawns an asymmetric pair of unstable equilibria. Continuing along this branch, there is a fold bifurcation (c) which stabilizes the symmetric state in which both populations are turned on. This state persists for all $d_{ei} < d_c \approx 3.62$. The effect of reducing the competition is that we enable the state in which both equilibria are turned on to be stable. We now pick up the pitchfork bifurcation at b. This pair of unstable branches representing an asymmetric case in which one population is more active than the other undergoes a fold bifurcation at d and gives rise to winner-take-all dynamics. For $d_{ei} > d_d \approx 1.162$ the network has a state in which one population is on and the other off. This corresponds to the normal state in which there is memory of the initial stimulus. A symmetric unstable branch of periodic orbits emerges from the Hopf bifurcation at a which undergoes a period-doubling bifurcation g. As we continue along the symmetric unstable branch of periodic orbits (green dashed) there is a fold of limit cycles (e) and the symmetric synchronous oscillation is stabilized (thick dark green curve). This solution remains until there is another fold (f) leading to an unstable synchro-

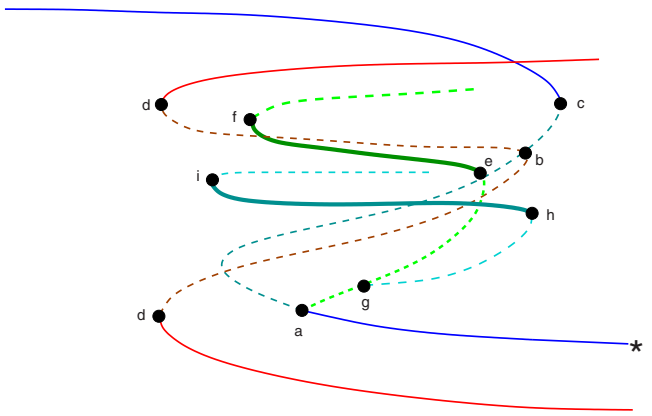



FIG. 5. (Color online) Schematic of the dynamics of a two-population network as the cross *E-I* strength is reduced. Solid thin lines correspond to stable fixed points (red/blue) and solid thick lines correspond to stable periodic behavior (green/cyan). Black filled circles are important bifurcations. Details are in the text.

nous solution (dashed green curve). Stable synchronous oscillations exist for a limited range of $2.077 \approx d_f < d_{ei} < d_e \approx 2.889$. Turning our attention to the period-doubling bifurcation (g) this branch of unstable asymmetric solutions (dashed, cyan) undergoes a fold bifurcation at h and another fold at i such that there are stable antiphase (alternating) oscillations for $1.85 \approx d_i < d_{ei} < d_h \approx 3.17$. It is rather remarkable that all these branches are connected. In the normal network, we imagine that $d_{ei} > d_c$ so that the only attractors are the quiescent state and the two fixed points corresponding to WTA behavior. The most pathological state occurs for $d_{ei} < d_d$ where only the completely excited state exists. These patterns correspond to the patterns of activity seen in the 20-population model. Symmetric solutions correspond to homogenous behavior such as the synchronous oscillations seen in Fig. 3. The antiphase oscillations are analogs of the clustered states seen in Fig. 3 and the WTA behavior corresponds to the normal network states such as seen in Fig. 1.

## B. Basins of attraction

In this section we apply a variety of stimuli to the network when $d_{ei}$ is fixed at a value of 2.6 where all six attractors are stable. We will apply periodic stimuli at different frequencies with different amplitudes to see if it is possible to switch to the active states from the quiescent state. There are many possible stimulus parameters to vary, so we will start with the following. We stimulate for 2 or 3 s at a variety of different frequencies and with different amplitude ratios between the two populations. Specifically, we set the excitation to a value of 1 in population one (called the *preferred* stimulus or population) and vary the strength of the stimulus in population two between 0 and 1 (the *nonpreferred* case).

Figure 6 shows the phase diagram of the steady state behavior as a function of the period (in seconds along the horizontal axis) and the magnitude of the nonpreferred stimulus along the vertical axis. The behavior and transitions appear to be very complex. For example, with a 2 s stimulus (a) at about 4 Hz, as the nonpreferred stimulus increases, there is winner-take-all behavior, antiphase oscillations, and synchronous oscillations. The three second stimulus (b) shows qualitatively similar behavior but there is a much larger set of initial data leading to synchronous oscillations. Whereas shorter stimuli require nearly identical preferred and nonpreferred inputs, with a longer duration, the basin for synchrony is quite large. With the longer duration stimuli, synchrony takes over much of the territory of the antiphase oscillations, while the antiphase oscillations invade the rest state territory. Presumably, the latter effect is due to the longer stimulus allowing a greater buildup of the facilitation, $w$, thus making some active state more likely. In Fig. 7, we show an expanded parameter scan within the green rectangle in Fig. 6(a). Based on this we suspect that the basins of these attractors are very complicated with riddled fractal structure. It seems that there is never a direct transition from synchrony to antiphase. The WTA behavior always seems to separate these two attractors. The complex behavior shown here is a consequence of the pathology introduced in the network. In the normal network, we find (not shown) that for all two

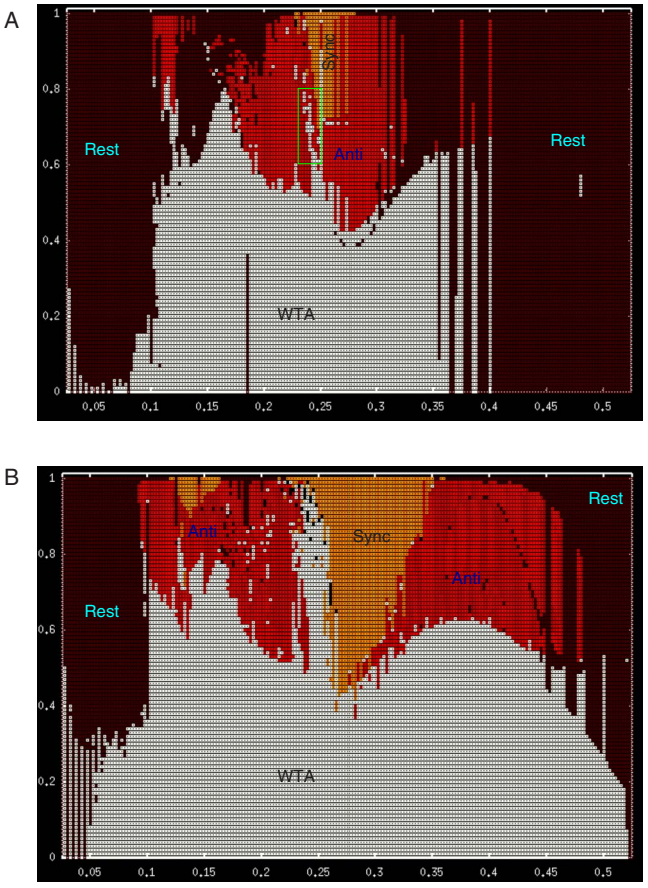



FIG. 6. (Color online) Steady state behavior of the pathological network (*E-I* cross connections reduced to 2.6) as a function the period of the stimulus (in seconds) and the strength of the nonpreferred stimulus (preferred strength is 1). Four colors correspond to four different states: Return to rest (brown), winner-take-all (white), synchronous oscillations (orange), and antiphase oscillations (red). (a) 2 s stimulus; (b) 3 s stimulus.

second stimuli (periods between 0.05 and 0.5 s), the network goes to the usual winner-take-all behavior with the preferred population always winning.

The steady state behavior is very difficult to predict by looking at the time series of the populations. Figure 8 shows the dynamics of the facilitation $w_1, w_2$ and the excitatory

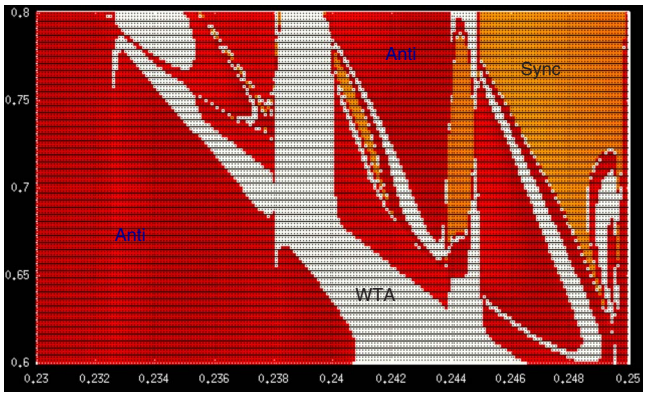



FIG. 7. (Color online) Expanded view of green rectangle in Fig. 6(a). Riddled basin for input stimuli in a narrow range of periods and relative amplitudes. Parameters are the same as in Fig. 6(a) in the region shown with the green box.

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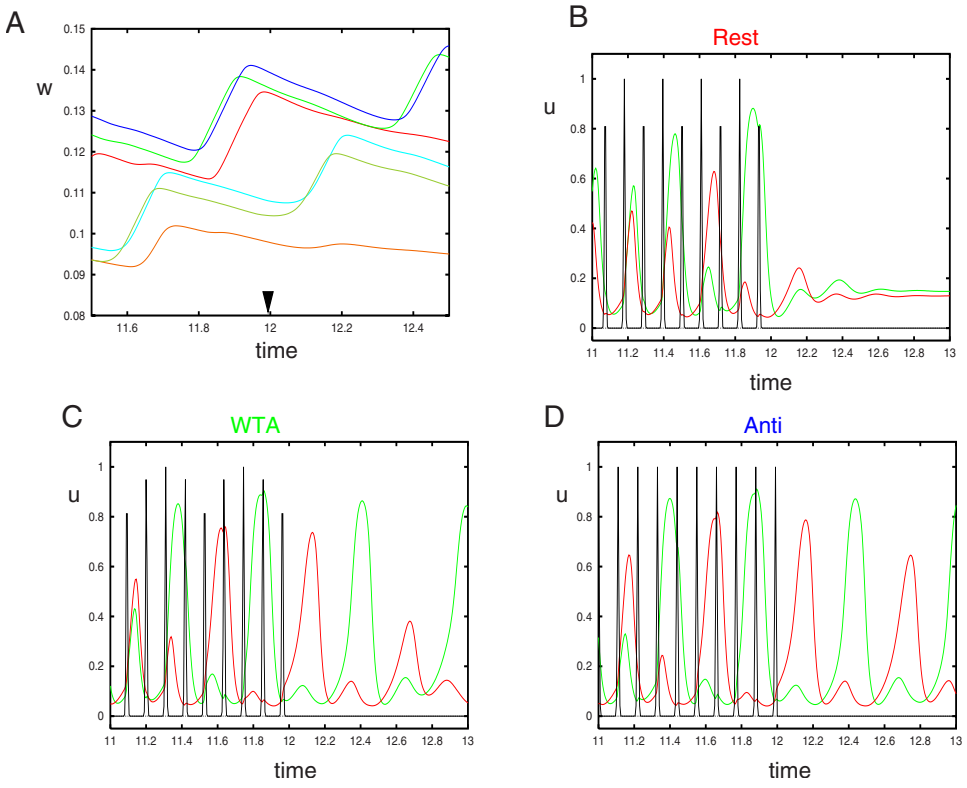


FIG. 8. (Color online) Behavior of the two-population network at the termination of a 2 s stimulus with different periods and with the nonpreferred amplitude of 0.8. (a) the facilitation variables $w_1, w_2$ at three different periods leading to three different states: green/olive (period of 0.108 75) WTA with green (preferred) winning; blue/cyan (period of 0.11) antiphase oscillations; red/orange (period of 0.1075) both die. (b) preferred (green), nonpreferred (red), and stimulus (black) when in the rest state basin; (c) same as (b) with WTA; (d) same as (b) when antiphase oscillation occurs.

activity $u_1, u_2$ of the two populations. In Fig. 8, we show these variables for a short period of time centered around the end of the stimulus. In all cases, the nonpreferred stimulus is 0.8 and the preferred is 1.0. We choose three different nearby periods for the stimulus such that there is either return to rest, antiphase oscillations or winner take all. Figure 8(a) shows the facilitation in the three cases. The red/orange curves correspond to a period of 0.1075 s and both populations return to rest. There simply is not enough buildup of $w_{1,2}$ to maintain them. The excitatory activity is shown in Fig. 8(b). The green/olive curves correspond to a stimulus period (0.108 75 s) in which there is WTA behavior with the preferred (green) population winning. Note that because the nonpreferred stimulus amplitude is smaller, the green curve is above the olive curve. The blue/cyan pair shows the preferred/nonpreferred when the system ends in the antiphase state (period of 0.11). Both curves are slightly higher than the green/olive combination due to the slightly higher frequency of stimulus. We first contrast the rest with the antiphase case. The facilitation of the second nonpreferred population (cyan) is quite a bit less than that of the preferred population in the rest case (red) and yet the nonpreferred population stays active after the stimulus. The reason for this is that the preferred adaptation variable (blue) is sufficiently high to turn on and the recurrent *E-E* connections between the two populations give the second population a boost. Indeed, just lowering this parameter ($d_{ee}$) from 0.7 to 0.6, pushes both populations to rest. The distinction between WTA and antiphase behavior is far less clear. Figures 8(c) and 8(d) show that the activities of the two populations (green is preferred; red is nonpreferred) are almost identical after the stimulus finishes and the first two cycles look like an antiphase oscillation. The difference between the adaptation variables at the end point of the stimulus is essentially the same. Thus, there seems to be little *qualitatively* different between the transition to WTA and to antiphase. This feature provides a potential explanation for the complex fractal nature of the basins of attraction shown in Figs. 6 and 7.

The two-population model shows very sensitive dependence on perturbations even though each of the attracting states is very robust. It is only possible to reach the upper state in which both populations are firing at a steady state when the stimuli to both populations are very strong and nearly symmetric.

## V. ONE POPULATION

Three of the behaviors described in Sec. IV can be understood by looking at the one-population model which is only a three-dimensional dynamical system. Furthermore, in fact, it is two fast variables $(u, v)$ and one slow variable ($w$, the facilitation) so that we can apply standard fast-slow decomposition methods. In the two populations (and in the $N$ population model), one can consider the following three cases: all at rest, synchronous oscillations, and all turned on. In each of these three cases, all populations are identical, so we are left with a three-dimensional system,

$$\tau_u \frac{du}{dt} = -u + f((a_{ee} + d_{ee})(1 + kw)u - a_{ie}v - \theta_e), \quad (4)$$

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$$\tau_v \frac{dv}{dt} = -v + f((a_{ei} + d_{ei})u - a_{ii}v - \theta_i), \quad (5)$$

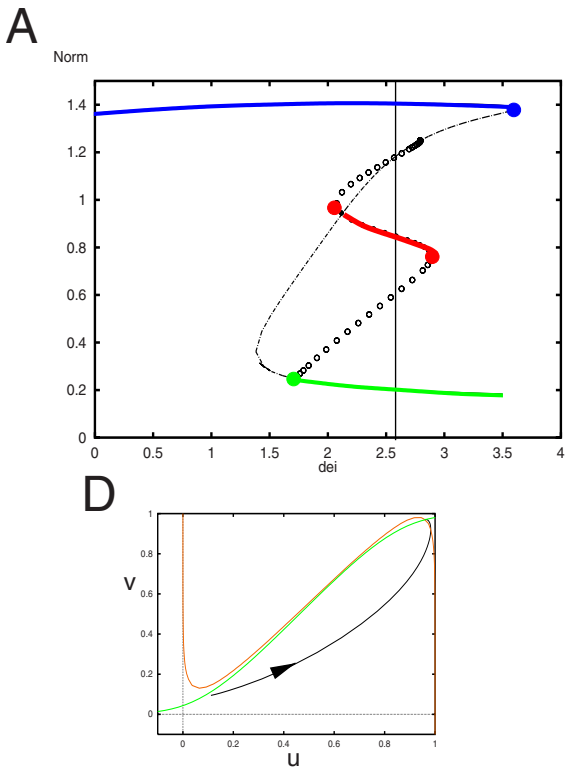


FIG. 9. (Color online) (a) Bifurcation diagram for the single population model as the cross inhibition $d_{ei}$ varies. Green curve is quiescent rest state, blue curve is the excited state, and red is a branch of periodic oscillations. Vertical line corresponds to $d_{ei}$=2.6. (b)–(d) represent phase planes of the $u$-$v$ system with $w$ frozen at the steady state or average value along the line in (a). (b) $w$ held at the value on the green curve, (c) red curve, and (d) blue curve.

$$\tau_w \frac{dw}{dt} = -w + f(\gamma(u-\theta_w))[w_{\max} - w]. \tag{6}$$

Here we retain the coupling parameters $d_{ee}, d_{ei}$ in order to emphasize that these equations represent the *symmetric solutions* of the coupled populations.

Figure 9 shows the bifurcation diagram for the three-dimensional model when $d_{ei}$, the cross $E$-$I$ coupling, varies. For large values, the only symmetric solution which exists is the quiescent state. As $d_{ei}$ decreases, there is a fold and the upper symmetric state (all-on) appears and remains stable for all lower values of $d_{ei}$. At $d_{ei} \approx 1.713$ the lower quiescent state loses stability at a subcritical Hopf bifurcation and then loses the existence at a fold. The subcritical branch of periodics turns around at $d_{ei} \approx 2.89$ and becomes a stable branch of periodic solutions. This branch again loses stability at a fold at $d_{ei} \approx 2.08$. Thus for $2.08 < d_{ei} < 2.89$ there is a stable periodic solution, two stable fixed points, two unstable periodic orbits, and an unstable fixed point. $w$ varies slowly due to its long time constant, and even on periodic branches, it varies only over a small range of values. We fix $d_{ei}$=2.6 and hold $w$ at its steady state or average values corresponding to the three stable behaviors shown in the bifurcation diagram. Figures 9(b)–9(d) show the phase-plane dynamics for the $u$-$v$ system with $w$ frozen. In each case, there is a unique stable attractor corresponding to the three states in the bifurcation diagram.

Treating $w$ as a parameter, we can write $u(t) = U(t;w)$, where $U$ is the solution along the bifurcation diagram in Fig. 9(a). Along the blue and green branches, $U$ is independent of time, and along the red branch, it is periodic. The slow $w$ dynamics evolve according to Eq. (3). Since $\tau_w$ is large, we replace $u$ by the steady state $U(t;w)$ and obtain

$$\tau_w \frac{dw}{dt} = -w + f(\gamma(U(t;w)-\theta_w))[w_{\max} - w].$$

We note that along the equilibrium branch, $U(t;w)$ is a function of $w$ only, so the right-hand side is only a function of $w$. Along the periodic branch, we can average and again obtain a function of $w$. Thus, we reduce the $w$ dynamics to an equation of the form

$$\tau_w \frac{dw}{dt} = -w + \langle f(\gamma(U(t;w)-\theta_w))[w_{\max} - w]\rangle$$
$$:= -w + G(w). \tag{7}$$

Thus, we can plot the average $G(w)$ evaluated along branches of the solutions to the fast $(u,v)$-dynamics with $w$ as a parameter. Figure 10 shows $G(w)$ versus $w$ for several values of $d_{ei}$ along with the identity line, $y=w$. Intersections of $G(w)$ with $w$ correspond to solutions to the full three-dimensional system which are either equilibria or periodic solutions. For example, with the normal value of $d_{ei}$=3.5, there are two stable solutions, one in which the network is quiescent and one in which the population is excited (lower and upper gray circles, respectively). As $d_{ei}$ is lowered, the curve of values $G(w)$ rises vertically and the middle branch (red) of stable periodic orbits intersects the diagonal line. This "fixed point" represents a stable branch of periodic solutions to the full model and a synchronous oscillatory solution to the full two (or more generally, $N$–)-population system. As can be seen from Fig. 10(b), where $d_{ei}$=2.6, there are six fixed points corresponding to the two stable resting states (left- and rightmost fixed points) and the synchronous orbit.

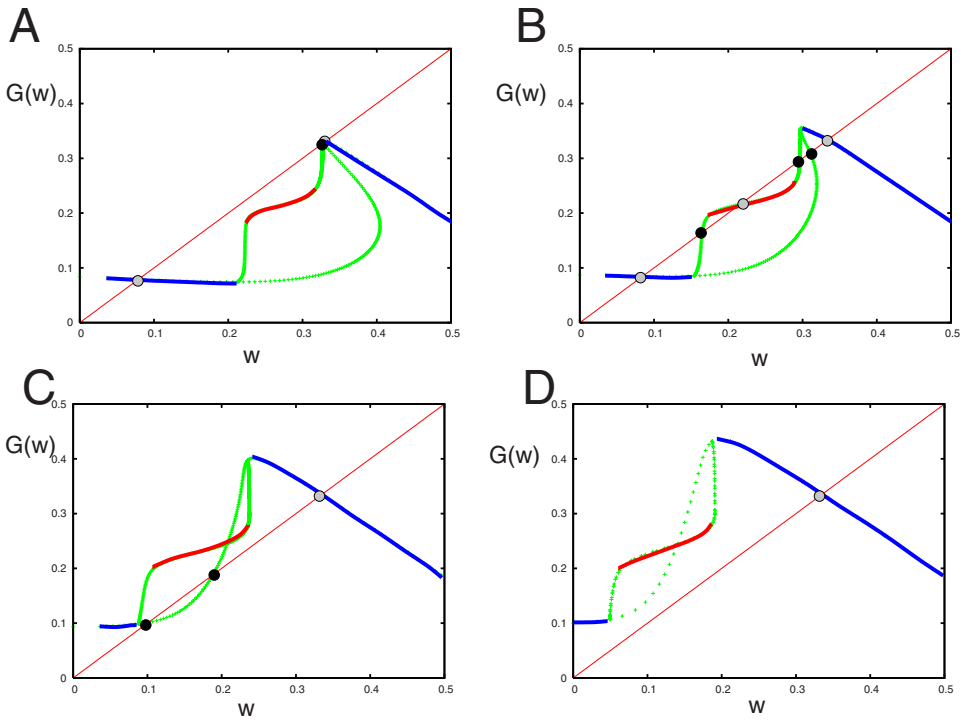


FIG. 10. (Color online) The curves depict $G(w)$ as a function of $w$. [See Eq. (7).] Blue curves are stable equilibria to the fast dynamics and red thick curves are stable periodic solutions. Gray circles correspond to stable solutions and black circles to unstable. Each diagram is for a different value of $d_{ei}$. (a) $d_{ei}$=3.5, (b) $d_{ei}$=2.6, (c) $d_{ei}$=2, and (d) $d_{ei}$=1.

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Consider again Fig. 9. The vertical line corresponds to $d_{ei}$=2.6. There are two unstable periodic orbits, one stable periodic orbit, two stable equilibria, and one unstable equilibrium just as would be predicted from the slow-fast decomposition in Fig. 10(b). As $d_{ei}$ is raised further to 2, the branch of periodics is lifted above the diagonal and the stable lower equilibrium point is shifted toward and onto the unstable equilibrium of the fast dynamics [see Fig. 10(c)]. The only stable solution to the three variable model is the upper active state. Finally, for $d_{ei}$=1, the only equilibrium, stable or otherwise, is the upper state.

We can also use this separation of time scales to understand the dependence on frequency of the stimulation. In particular, we can see why very fast and very slow stimuli are ineffective in exciting the network. Figure 11(a) shows the evolution of the facilitation $w$ for four different periods of input lasting a total of 10 s each for somewhat reduced inhibition ($d_{ei}$=3). Only the stimulus with period of 0.3 s is sufficient to push the network into an excited state. In this reduced inhibition case, the fast subsystem (holding $w$ at its resting value) is an excitable medium; there is a stable rest state but amplification before return to rest. Once the popu-

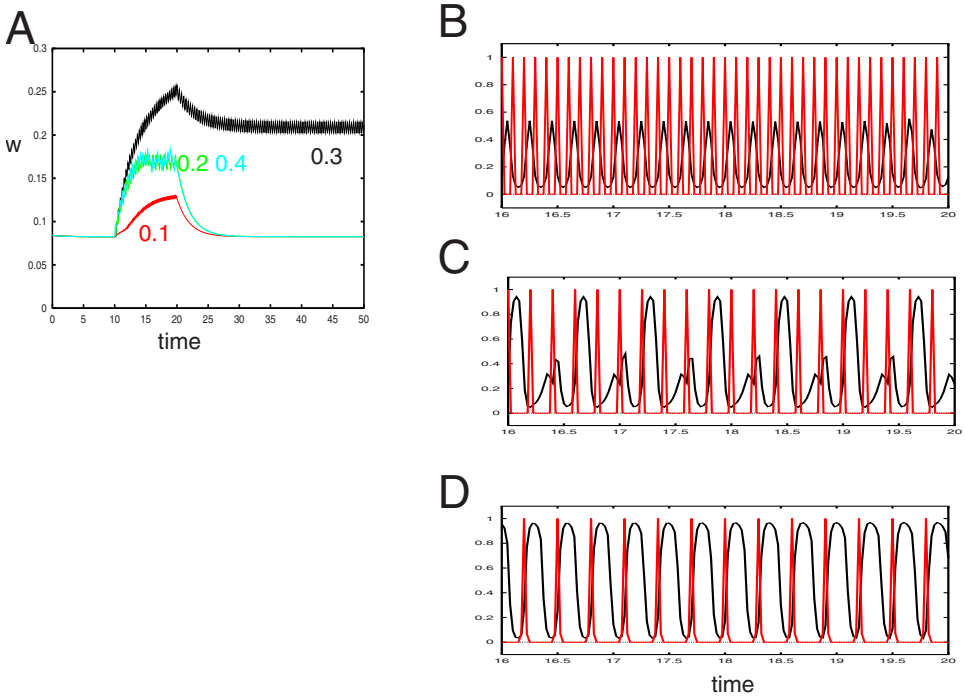


FIG. 11. (Color online) (a) The evolution of $w$ during periodic stimuli lasting 10 s. Period of the stimulus is shown next to each curve. (b) and (c) Evolution of $u(t)$ during stimuli (red curves show the periodic stimulus) for periods of 0.1,0.2, and 0.3 s.

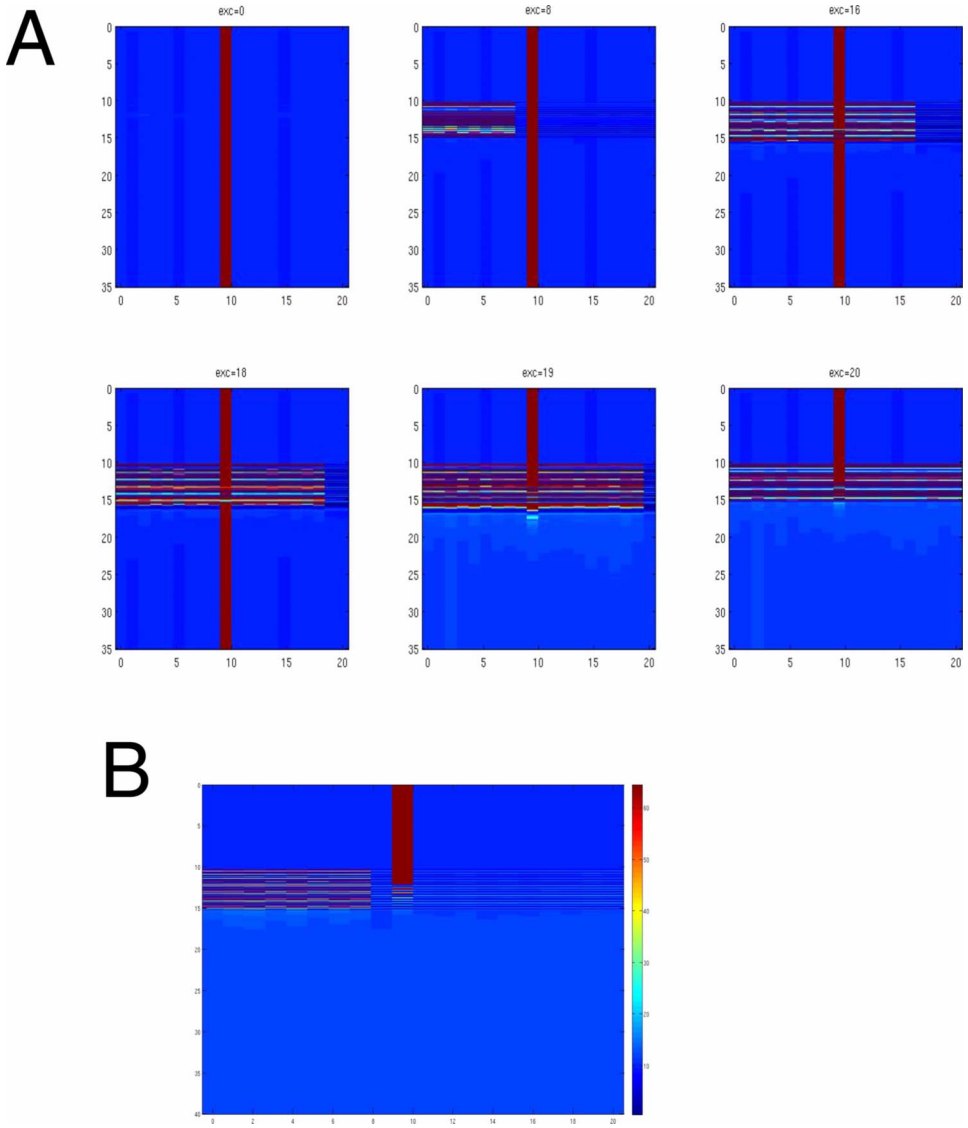


FIG. 12. (Color online) Terminating the activity of a single active population under full inhibition ($d_{ei}$=5.4). Panel (a) shows the effect of stimulating the first $k$ populations. Notice how the active population (number 10) only goes back to baseline when 19 or 20 populations are stimulated. Panel (b) shows the same network with the same initial state, but in this case the inhibitory component of population 10 is stimulated along with the first eight populations. In both cases the frequency of the stimulus is 3.3 Hz.

lation is excited, however, it needs time for the inhibition to wear off before it is excited again. Thus, if the frequency of the stimulus is too high, the population can either never fire again or fire only on a fraction of the cycles [cf. Figs. 11(b) and 11(c)]. However, at a low enough frequency, the excitatory population fires at every cycle [Fig. 11(d)] allowing the facilitation to build up and affect the switch into an excited state. For lower frequencies, 1:1 locking still occurs and the excitatory population fires on every cycle, but the time between firing is such that the $w$ can never reach a sufficient level to push the medium into an excited state. Thus, for intermediate frequencies, we can push the network into an excited state.

## VI. SEIZURE TERMINATION

A working memory network would be of no use if the persistent activity of its populations could not be terminated. It is therefore pertinent to study how the states which are reached after the stimulation of the network can be reverted back to the baseline state using a second stimulus. We study termination in three general cases: first during normal network behavior, when inhibition has not been disrupted, and there are only one or two populations active simultaneously. The second case we study is when inhibition has been disrupted so that there are multiple populations displaying high activity, and the third case addresses the termination of oscillatory behavior. These last two could also offer some insight into possible mechanisms for the termination of ictal activity.

In the case with normal inhibition there are several ways to revert the state back to baseline. The most straightforward one consists of exciting all the populations so that lateral inhibition shuts down the active one (Fig. 12). This method of terminating the activity is fragile, since any reduction in the inhibition will render it ineffective, and it requires the activation of nearly all populations. Moreover, there is again frequency sensitivity, with some frequencies of the stimulus being better suited to turn down the activity. Increasing the duration of the stimulus is a way to enlarge the range of frequencies that can turn down the activity. Combining selective stimulation of the inhibitory component of the active population with the stimulation of the rest of the populations largely reduces the number of populations which need to be

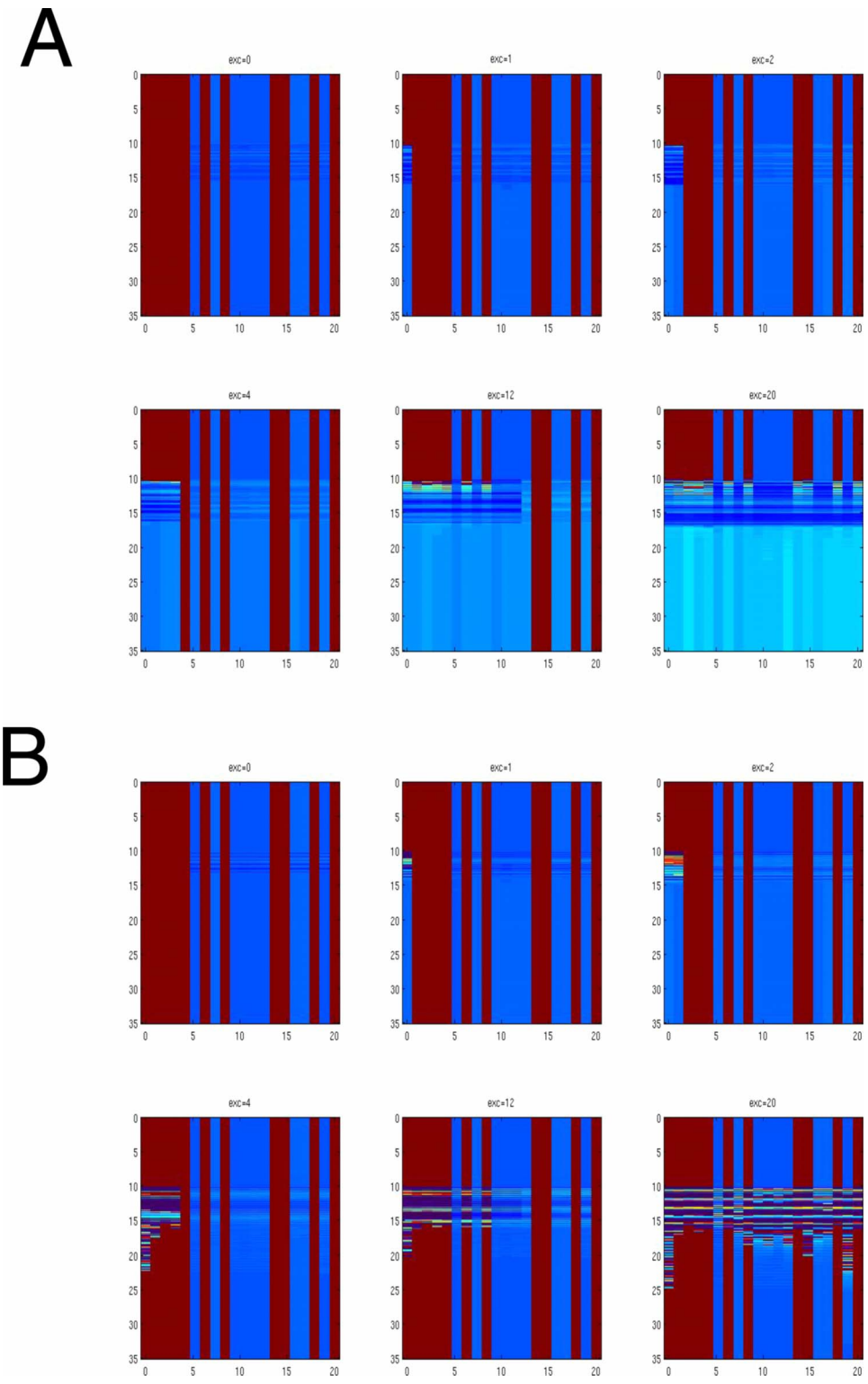


FIG. 13. (Color online) A network with low inhibition ($d_{ei}$=1.59) and many excited populations may be reset to baseline using inhibitory inputs to the excited populations. The left panel shows a 10 Hz inhibitory stimulus being applied to 0, 1, 2, 4, 12, and 20 populations, starting with the leftmost one. The panel on the right is similar, but the stimulus has a frequency of 3.3 Hz. Note that in the left panel whenever a population is inhibited it goes to baseline, whereas in the right panel this only happens when the number of populations inhibited is small.

stimulated and allows termination with a broader set of frequencies (Fig. 12).

In the case where we have a large number of populations active simultaneously (following a breakdown of inhibition), it is no longer possible to turn down the activity by exciting all populations (this may result in more populations becoming active). In fact, when the inhibition has been reduced to the point where exciting one population may recruit several others, the direct stimulation of the inhibitory component of the active populations is not sufficient to turn them off; a direct inhibitory stimulus to the excitatory component of the active populations is required in order to terminate the activity (Fig. 13). Terminating the activity one population at a time requires less inhibition than the simultaneous termination of all activity. As in the prior case, the result of the stimulation is frequency dependent.

Unlike the case where we have a large group of active populations, both synchronous and antiphase oscillatory be-

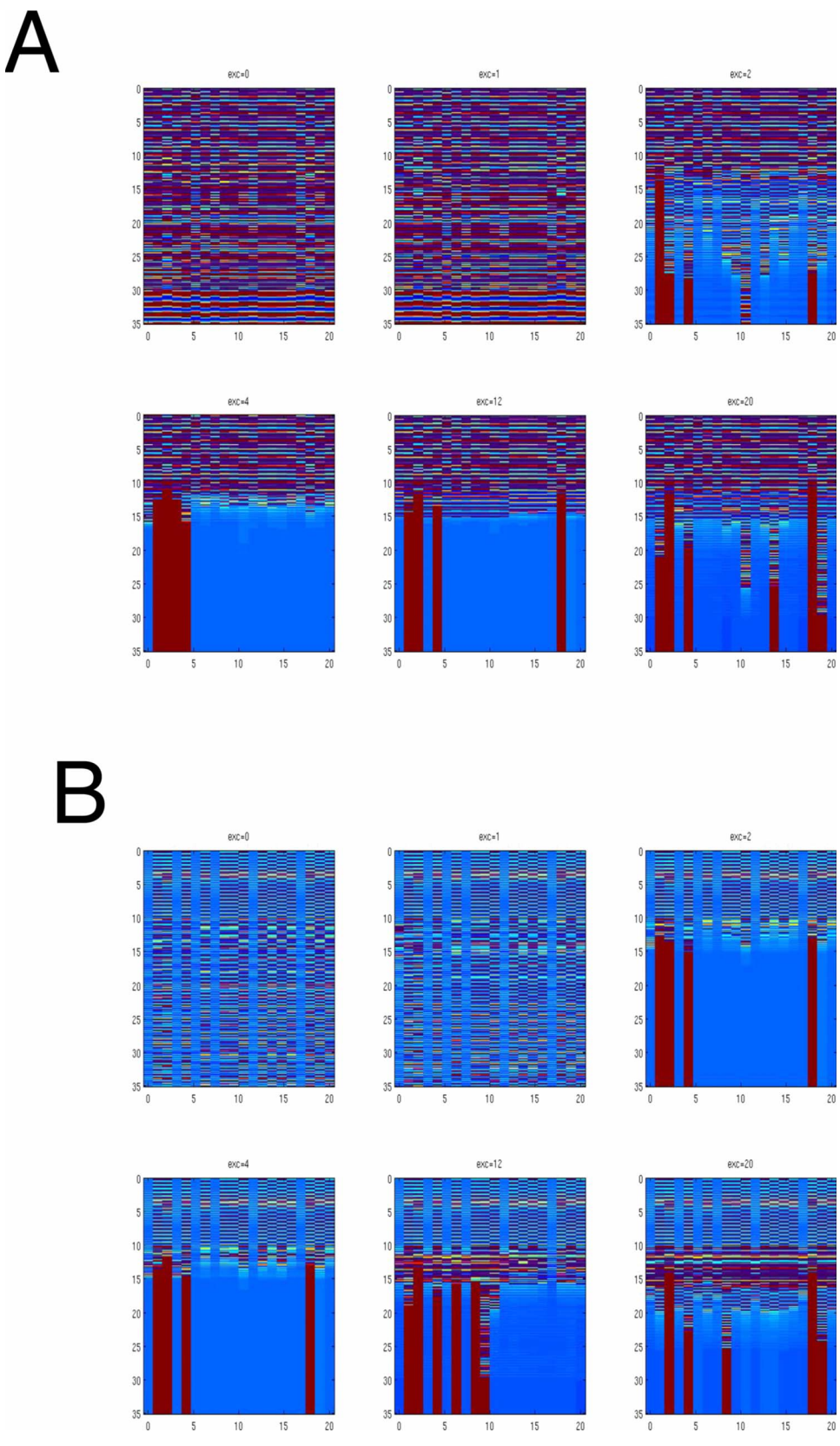


FIG. 14. (Color online) Oscillations can be terminated through the application of an excitatory stimulus to the excitatory and inhibitory components of a set of populations. The left panel shows the stimulus being applied to 0, 1, 2, 4, 12, and 20 populations in a network initially displaying synchronous oscillatory behavior. The right panel shows the same stimuli being applied to a network initially displaying antiphase oscillations. In both cases the frequency of the stimulus is 3.3 Hz and the inhibition is $d_{ei}$=2.

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havior can be turned off by a purely excitatory stimulus applied to a subset of the populations (Fig. 14). Depending on the amount of inhibition present and on the strength of the stimulus, the network state may evolve into one with many active populations. That is, the transition from oscillations may not necessarily take the system back to rest. This phenomenon can be understood using the fast-slow decomposition in the one-population model of Sec. V. When a subset of the populations is excited, lateral inhibition to the rest of the populations is created along with the excitation. If the net effect is inhibitory, the average value of the variable $u$ during the limit cycle to will drop down [Figs. 9(b) and 9(c)], and if

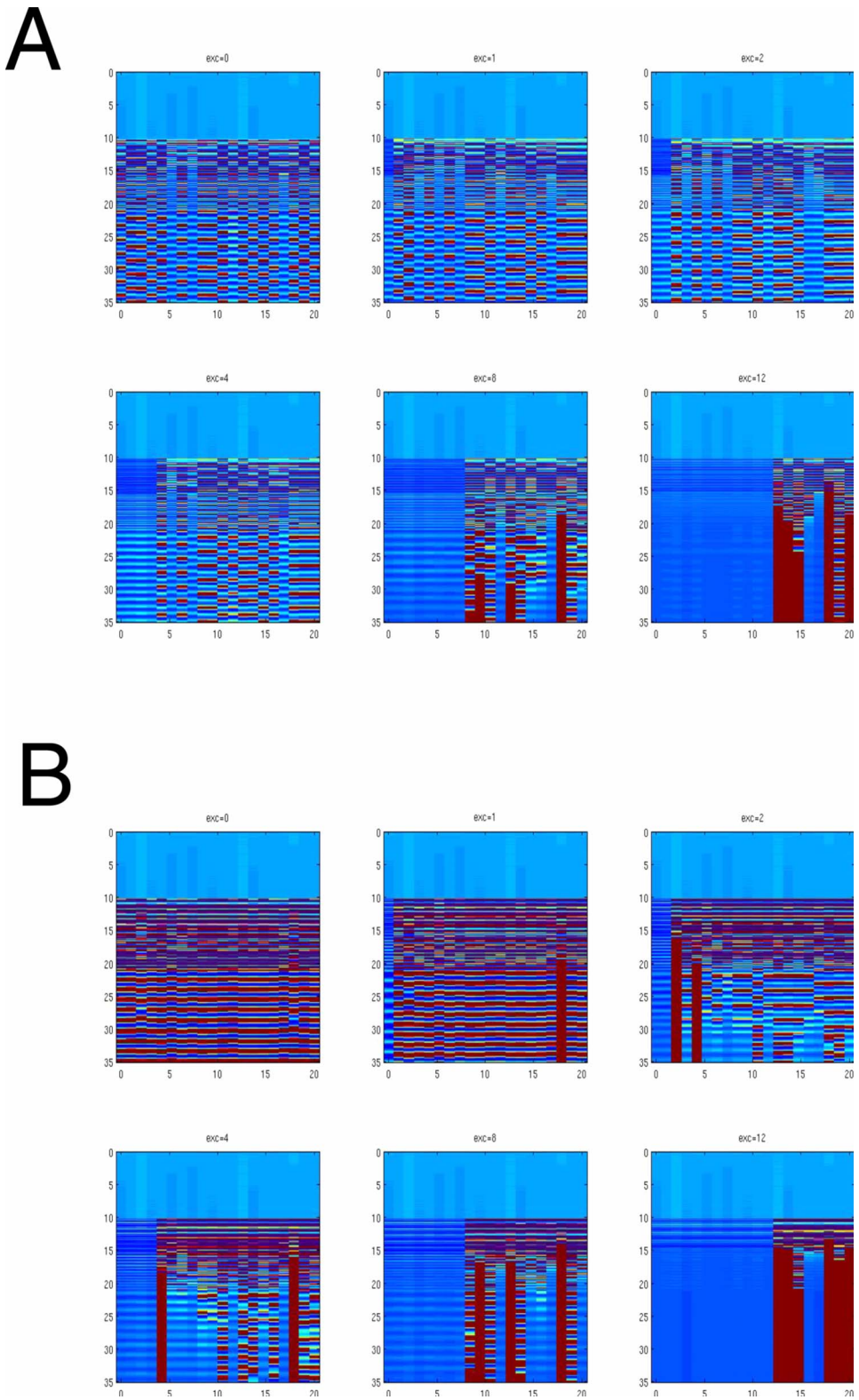


FIG. 15. (Color online) The onset of oscillations can be prevented when a certain number of populations receive a larger excitation than the rest in a case of low inhibition ($d_{ei}$=2). In panel (a) there are 0, 1, 2, 4, 12, or 20 populations receiving the larger stimulus which tends to prevent synchronous oscillations (notice how the system goes into synchronous oscillations when no populations receive the large stimulus). In this case the stimulus frequency is 3.3 Hz. Panel (b) is analogous to panel (a), but the stimulus frequency is 5 Hz, which tends to drive the network into antiphase oscillations.

it is excitatory the average value of $u$ will increase. The change in the average value of $u$ will cause the variable $w$ to, respectively, decrease or increase, and that change will lead it away from the basin of attraction of the oscillatory regime [Fig. 10(b)]. Once a few populations stop oscillating the generalized oscillations are no longer stable, and each population falls into one of the stable attractors left, usually baseline or high activity.

In addition to terminating oscillating behavior once it has been initiated, it is interesting to observe that the onset of oscillations can be prevented by applying a strong excitatory stimulus to some of the populations along with the stimulus which would otherwise cause all the populations to oscillate, as can be observed in Fig. 15. This phenomenon is not puzzling if we once again consider the fast-slow analysis of Sec. V and notice how the appearance of stable oscillations (Fig.

10) requires a balance in the average values of the $u$ variables: Stimuli which are too strong or too weak cannot lead the system into stable oscillations.

## VII. DISCUSSION

This work presents a physiologically based model of working memory yielding a potential generalized description of epilepsy or seizurelike behavior. The basic premise is that seizures result from inherent states in working memory networks that come about through disinhibition in the neuronal populations (either inherent imbalances between excitatory and inhibitory synapses or damage) resulting in a loss of population selectivity and potentially, concomitantly, a loss in stability of fixed point attractors. A critical component of the working memory network is dynamic synapses through facilitation which in normal working memory regions of parameter space enables the stable selective activation—to a particular input stimulus—of a given population. Changes in model parameters, however, specifically reduction in interpopulation inhibition, produce a series of bifurcations such that both normal and pathological states coexist for the same network parameter settings and external input (or internal perturbations) can trigger transitions from normal working memory to seizurelike behavior. Specifically here we consider a model indicative of a common type of reflex epilepsy, in which rhythmic stimulus input to hyperexcitable cortex produces seizures.

The network was not designed or fined tuned to exhibit seizurelike or ictal activity, but rather such states and behaviors are inherent over wide ranges of the parameter space of the normal working memory network. The network exhibits working memory behavior with sufficient lateral inhibition strength between populations. Following a typical working memory paradigm, there is a baseline period during which the network populations reside in a stable attractor and exhibit resting-state firing-rate levels. During presentation of a stimulus—which is to be held active in short-term memory—there is an external input (representing the stimulus) to the network populations that subsequently causes an increase in firing frequency. After this, the external input is terminated, and a delay period ensues in which the information about the stimulus must be retained ultimately for use in some subsequent behavioral or motor response. During this delay period, a specific population (or subset of populations) representing the stimulus information being held maintains persistent activation (above-baseline elevated firing rate). The network exhibits specificity in two ways. First only a given population becomes activated (i.e., winner-take-all) as a result of the afferent memorandum stimulus. Second, whether or not the population becomes active is a function of the particular frequency of the input. Thus specific frequencies of inputs represent a memorandum, and a particular population responds to that input preferentially and becomes persistently activated, while the activity of other populations remains at baseline levels. Further this working memory activity of the network reproduces the persistent patterned behaviors and firing statistics observed in real cortical cell populations recorded during the performance of working memory tasks. These results are presented elsewhere (Verduzco-Flores *et al.*, unpublished). The canonical working memory activity can be seen to be present from the schematic of the bifurcation diagram of the two-population model for sufficiently high values of the lateral inhibition. As inhibition is reduced, while working memory behavior is still present, multiple potentially pathological states that the network may adopt as a result of specific stimuli become possible through a series of bifurcations.

Epilepsy has previously been suggested to be a dynamical disease and previous work has suggested dynamical processes leading to seizure generation including deformation of system attractors induced by changes in network parameters that lead from normal to ictal activity, bifurcations in a system possessing both normal and pathological states coexistent for the same parameter setting such that external input or internal perturbations trigger sharp transitions from normal to epileptic behavior, and a mixture of both scenarios with gradual parameter variations facilitating the transition from normal to an ictal state (Lopes da Silva *et al.*, 2003). In the present work, we concentrate on the second of these (the coexistence of normal and pathological states). However all three of these routes to seizures are present in the model. Particularly facilitation in the model can create changes in the relative excitation and inhibition of the model which results in a deformation of the attractor structure.

We consider pathological activity in this work, specifically seizure activity, to be a loss of selectivity. That is, the ability of a specific subset of populations to become activated by a given stimulus input breaks down, and multiple populations are recruited by the stimulus in a nonlinear fashion. This is the general and perhaps the most common trait of all seizures and types of epilepsy. In the network we see that the recruitment of populations in pathological activity is such that different stimuli induce a loss of selectivity, with the number of populations activated (the degree of spread of the seizure) increasing in a nonmonotonic fashion. While synchronous activity of multiple populations has been implicated in normal cognitive function, it can be a double edged sword when that activation spreads. The dynamics under which normal binding and pathological recruitment and loss of selectivity occurs is as yet not understood. The elucidation of these mechanisms can lead to a better understanding of how seizures propagate and might be controlled. The specific dynamics exhibited by the activated pathological network are such that they can exhibit a range of population activities which include fixed firing rates, synchronous oscillations, and antiphase oscillations. Such varied states are typical of seizure in different types of epilepsies or indeed might be observed within a given seizure (Franaszczuk *et al.*, 1998). In the present model, the populations of the working memory networks can transition to all of these varied behaviors.

In the model, recruitment can occur along a range of different paths exhibiting different dynamics. As can be seen from the schematic of the bifurcation diagram of two interconnected populations (Fig. 5)—which generalizes to many populations—as inhibition is decreased the stable fixed firing rest state undergoes a Hopf bifurcation that after a pitchfork bifurcation ultimately (after a further fold bifurcation) results in winner-take-all working memory behavior. Thus normal

working memory behavior is still possible in the deranged network. This is indeed the case in human epilepsy in which seizures do not occur the majority of the time. However, it is also possible from the Hopf bifurcation, for the network to proceed to a state in which all the populations of the network are active exhibiting synchronous or antiphase oscillations. Thus the ultimate seizure state may involve hypersynchronicity, weak synchronicity, or periodic behavior depending on the specific network parameters.

A vital component of the present model is that transitions to specific states can be a function of the periodicity of the external stimulus. The dependence of transitions to a seizure-activity attractor on frequency relates to a model of reflex epilepsy. That is, epilepsies involve seizures resulting from exposure to a particular external or internal stimulus (often periodic). Facilitation and dynamic synapses which have been implicated in working memory here play a central role in which resonance with a given external stimuli causes pathological activity (Verduzco-Flores *et al.*, unpublished; Barak and Tsodyks, 2007). This has been suggested to be important in working memory networks. Structural changes and particular inputs can cause the dynamic synapse mechanisms to play a fundamental role in changing the state from one attractor to another (acting as a switch), going from normal to pathological activity. The fact that such a high percentage of people exhibit a seizure in their lifetime without developing epilepsy may indicate that this is an inherent feature. More permanent parameter changes caused, for example, through learning or trauma might bias activity toward the pathological region of the state space.

An understanding that all of these behaviors can be inherent in working memory networks and how they are related might lead to potential therapeutic interventions. In the model of reflex epilepsy presented here, we see that while pathological activity is induced by specific stimuli, we also see that specific inputs are capable of terminating seizure activity once initiated or prevent seizures from occurring depending on the specific dynamics of the seizure. In the case of termination of seizure activity once initiated, this may have relevance to the mechanisms involved in recent attempts to control seizures through electrical stimulation of the cortex (Ben-Menachem, 1996; Labar *et al.*, 1999; Morris and Mueller, 1999; Velasco *et al.*, 1995, 2000). In Fig. 14 we show that a general excitation of the populations, when the specific dynamics of seizure activity involves oscillations (synchronous or asynchronous), results in the termination of the seizure. Specifically from the schematic of the bifurcation diagram, we see that the general stimulation induces a transition from the stable synchronous oscillation state to the baseline state through modulation of the facilitation. Thus, electrical stimulation may be most efficacious in treating seizures with that particular type of dynamics. In the case of prevention of seizure activity, recently evidence has been accumulating, indicating that stimulation of the cortex with specifically patterned sensory input (i.e., particular music) can reduce or eliminate pathological interictal activity with a resulting reduction or even elimination of seizures in particular cases (Hughes *et al.*, 1998, Hughes and Fino, 2000; Shaw and Bodner, 2005; Turner, 2004a, 2004b; Lahiri and Duncan, 2007). The mechanism for this intervention might be related to the dynamics examined in Fig. 15. Here we see that the excitation of multiple populations by inputs of specific frequencies prevents the transition of the network to a pathological state (elaborate on the specific states/attractors?). This models the activity of the musical stimulus which has been demonstrated to strongly excite a widely distributed population of neurons associated with working memory networks (Bodner *et al.*, 2001; Muftuler *et al.*, 2004). Recent evidence has indicated that long term exposure may result in a long-term shifting of the attractors away from pathological states.

## ACKNOWLEDGMENTS

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