likely, and [26] suggests that weak and aperiodic stimulation of interneurons is the best protocol to make this distinction. Nonetheless, it is clear that recent experiments have verified much of the extensive theory developed regarding the mechanism of gamma rhythms.

One particularly notable experimental observation of the PING mechanism for gamma rhythms is that constituent excitatory neurons fire sparsely and irregularly [12,27], while inhibitory neurons receive enough excitatory input to fire regularly at each cycle. Due to their possessing slow hyperpolarizing currents, pyramidal neurons spike more slowly than interneurons [28], so this partially explains their sparse participation in a fast rhythm set by the interneurons. Modeling studies have accounted for the wide distribution of pyramidal neuron interspike intervals by presuming sparse random coupling in network connections [29] or by including some additive noise to the input drive of the population [30]. From this standpoint, the excitatory neurons are passive participants in the generation of fast rhythms, so their statistics have no relation cell to cell. The requirement, in these cases, is a high level of variability in the structure and drive to the network. However, an alternative explanation of sparse firing might suggest that excitatory neurons assemble into subpopulations, $cl\ \ e$, that fire in a more regular pattern for a transient period of time. This may be accomplished without the need for strong variability hardwired into a network.

One cellular mechanism that has been largely ignored in network models of fast synchronous spiking rhythms is spike frequency adaptation [30,31]. Slowly activated hyperpolarizing currents known to generate spike frequency adaptation have been shown in many different populations of regular spiking cells within cortical areas where gamma rhythms arise. In particular, pyramidal neurons in visual cortex exhibit slow sodium and calcium activated afterhyperpolarizing current, proposed to play a major role in generating contrast adaptation [32]. Regular spiking cells in rat somatosensory cortex also have adaptive currents. Furthermore, they exhibit a type 1 threshold, where they can fire regularly at very low frequencies [33]. Also, recent experiments in primate dorsolateral prefrontal cortex reveal significant increases in interspike intervals due to spike frequency adaptation [34]. Synchronous spiking in the gamma range has been observed in visual [2,12], somatosensory [35,36], and prefrontal [14] cortex, all areas with neurons manifesting adaptation. Also, adaptation may promote a low resonant frequency in regular spiking neurons that participate in gamma rhythms, as revealed by optogenetic experiments [24]. Therefore, adaptation not only slows the spike rate of individual regular spiking neurons, but can play a role in setting the frequency of network level spiking rhythms.

Thus, we propose to study a paradigm for the generation of a network gamma rhythm in which excitatory neurons form clusters. This accounts for the key observation that excitatory cells do not fire on every cycle of the rhythm. The essential ingredients of the network are spike frequency adaptation and global inhibitory coupling. Spike frequency adaptation produces the slow firing of individual cells. The restrictions on the sparsity of coupling and the level of noise in the network are much looser than [30]. After identifying these properties of the network, we can extract several relationships between parameters of our model and attributes of the resulting clustered state of the network. One result of considerable interest is the relationship between the time constant of adaptation and the number of clusters that can arise in the network. Using two different methods of analysis, we can predict the cluster number N_c to scale with adaptation time constant $_a$ as $N_c \propto {}_a^{2/3}$.

The paper employs both a detailed biophysical model as well as an idealized model that we study for the formation of cluster states. Our results begin with a display of numerical simulations of cluster states in the detailed model. The main point of interest is that excitatory neurons possess a spike frequency adaptation current whose timescale appears to influence the number of clusters that can arise. To begin to understand how this happens, we analyze the periodic solution of a single adapting neuron, in the limit of large adaptation time constant, for an idealized model of adapting neurons. Using singular perturbation theory, we can derive an approximate formula for the period of a single neuron and thus an estimate of the number of clusters in a network of neurons. Then, an exact expression is derived for the periodic solution of an equivalent quadratic integrate and fire model with adaptation as well as its phase-resetting curve. Next, we employ a weak coupling assumption to predict the number of synchronized clusters that will emerge in the network as the amplitude of additive noise is decreased. The number of clusters in the predicted state is directly related to a Fourier decomposition of the phase-resetting curve. Our main result is that both the singular perturbation theory and weak coupling analysis predict the same $2/3$ power law relating cluster number to adaptation time constant. Finally, we compare our predictions made using singular perturbation theory and the weak coupling approach to numerical simulations of the idealized model and the detailed biophysical model.

Traub model of an excitatory-inhibitory network with adaptation

For our initial numerical simulations, we use a biophysical model developed by Traub for a network of excitatory and inhibitory spiking neurons [37]. Parameters not listed here are given in figure captions. The membrane potentials of each excitatory neuron and each inhibitory neuron satisfy the dynamics:

$$C\frac{dV_j^e}{dt} = -I_{e-ion}(V_j^e) - I^{ee}$$

$$I_j^{ee} = \sum_{k=1}^{N} G_{jk}^{ee} s_e^k (V_e^j - V_{syn}^e), \quad j = 1,...,N,$$

$$I_j^{ei} = \sum_{k=1}^{M} G_{jk}^{ei} s_i^k (V_i^j - V_{syn}^i), \quad j = 1,...,N,$$

$$I_j^{ie} = \sum_{k=1}^{N} G_{jk}^{ie} s_e^k (V_e^j - V_{syn}^e), \quad j = 1,...,M,$$

$$I_j^{ii} = \sum_{k=1}^{M} G_{jk}^{ii} s_i^k (V_i^j - V_{syn}^i), \quad j = 1,...,M,$$

where G^{ee}, G^{ei}, G^{ie}, and G^{ii} are random binary matrices such that

$$\Pr(G_{jk}^{ee} = 1 \text{ mS/cm}^2) = g_{ee}, \quad j = 1,...,N,$$

$$\Pr(G_{jk}^{ei} = 1 \text{ mS/cm}^2) = g_{ei}, \quad j = 1,...,N, \quad k = 1,...,M$$

$$\Pr(G_{jk}^{ie} = 1 \text{ mS/cm}^2) = g_{ie}, \quad j = 1,...,M, \quad k = 1,...,N$$

$$\Pr($$

Random initial conditions are used for the simulations of the model, and we wait until the system has settled into a steady state to make calculations of the statistics. We evolve this model numerically, using the Euler-Maruyama method, with a time step of dt = 0.0001.

Idealized model network with adaptation

The majority of our analysis uses an idealized spiking neuron model to study the mechanism of clustering associated with a network of adapting neurons. The Traub model for a single neuron exhibits a saddle-node on an invariant circle (SNIC) bifurcation. It is possible to exploit this fact to reduce the Traub model to a theta neuron model with adaptation, if the system is close to the bifurcation and the adaptation is small and slow [38]. In [39], an alternative conductance based model with an afterhyperpolarizing (AHP) current was reduced using phase reduction type techniques, where the AHP gating variable was taken to evolve slowly. In particular, Fig. 3(c) of [39] shows that the associated phase-resetting curve has a characteristic skewed shape. We also eliminate the inhibitory cells from the idealization of this section by slaving their synaptic output to the total firing of the excitatory cells. To our knowledge, there is no rigorous e k level reduction that would allow us to reduce the excitatory-inhibitory conductance based network to the idealized one we present here. We do not provide a meticulous reduction from the Traub network model to the network analyzed from here on. We do wish to preserve the essential aspects of the biophysical model described in the previous section, spike frequency adaptation and inhibitory feedback.

Therefore, we consider a system of N spiking neurons, each with an associated adaptation current, globally coupled by a collective inhibition current

$$\dot{\theta}_j = 1 - \cos\theta_j + (1+\cos\theta_j)(I + \quad_j - z_j - s), \qquad \text{ð1aÞ}$$

$$\epsilon_a \dot{z}_j = -z_j + \epsilon_a \, (\quad - \theta_j), \qquad \text{ð1bÞ}$$

$$\epsilon_s \dot{s} = -s + \frac{1}{N}\sum_{j=1}^{N} (\quad - \theta_j), \qquad \text{ð1cÞ}$$

for j =

sort function. We do not resort the neurons between the left and right panel, which displays the mixing effects of cycle skipping.

We use standard techniques for computing the interspike interval

where $\underline{N_c}$ and $\bar{N}_c$

connectivity for generating sparse firing. This can be contrasted with the degradation of correlations between excitatory neurons on fast timescales in [30], due to strong fluctuations and sparse connectivity in their excitatory-inhibitory network.

Thus, the cluster state that arises in this biophysically based network of spiking neurons appears to be a stable state that exists over a large range of parameters. The essential ingredients are a slow adapting current and inhibitory neurons that only fire when driven by excitatory neurons.

Analysis of clustering mechanism in an idealized network

The key feature of the detailed biophysical model that makes excitatory neurons susceptible to grouping into clusters is spike frequency adaptation. Few studies have examined the effects of adaptive mechanisms on the dynamics of synchronous states in spiking networks. In a study of two coupled adapting Hodgkin-Huxley neurons, their excitatory synapses transitioned from being desynchronizing to synchronizing as the strength of their spike frequency adaptation was increased [50]. In a related study, spike frequency adaptation was shown to shift the peak of an idealized neuron's phase-resetting curve, creating a nearly stable synchronous solution [51]. The effects of this on network level dynamics were not probed, and, in general, studies of the effects of adaptation on dynamics of large scale neuronal networks are fairly limited. A large excitatory network with adaptation can exhibit synchronized bursting, followed by long periods of quiescence set by the adaptation time constant [52]. Spike adaptation must build up slowly and be strong enough to keep neurons from spiking at all. More aperiodic rhythms were studied in populations of adapting neurons by [53], who showed the population frequency could be predicted by the preferred frequency of a single adapting cell. Adaptation has also been posed as a mechanism for disrupting synchronous rhythms in [54], where increasing the conductance of slow hyperpolarizing currents transitions a network to an asynchronous state. There remain many open questions as to how the strength and timescale of adaptive processes in neurons contribute to synchronous modes at the network level.

We therefore proceed by studying several characteristics of the cluster state as influenced by spike frequency adaptation. First, we study how the period of a single neuron relates to the strength and time scale of adaptation. Then, we find how these parameters bear upon the number of clusters arising in the network of adapting neurons with global inhibition. Approximate relations are derived analytically and then compared to the results of simulations of (1) as well as the Traub model.

Approximating the periodic solution and cluster number with singular perturbation theory

We first present a calculation of the approximate period T of a single adaptive neuron, uncoupled from the network. The singular perturbation theory we use relies upon the fact that the periodic solution is composed of three different regions in time: an initial inner boundary layer; an intermediate outer layer; and a terminal inner boundary layer. In this case, the initial and terminal boundary layers correspond to what would be the back and front of an action potential in a biophysical model of a spiking neuron, such as the Traub model. The intermediate layer corresponds to a refractory period imposed by the strong slow afterhyperpolarizing current. An asymptotic approximation to the periodic solution is pictured in Fig. 3, showing the fast evolution of θ in boundary layers and slow evolution in the outer layer. The slow timescale arises due to the fact that $\epsilon_a \gg 1$, so we shall use the small parameter $\epsilon = 1/\epsilon_a$ in our perturbation theory. Key to our analysis is the fact that the end of the outer layer comes in the vicinity of a saddle-node bifurcation in the fast subsystem, determined by the θ equation (1a). It then turns out that, as a result, we must rescale time to be $\tau = O(\epsilon^{1/3})$ in the terminal boundary solution. Such an approach has been studied extensively by Guckenheimer in the Morris-Lecar and Hodgkin-Huxley neurons with adaptation, as well as general systems that support canards of this type [55,56]. Nonetheless, we proceed by carrying out a similar calculation here and use it to derive an approximate formula for the period of the solution. We find that it matches the numerically computed solution remarkably well. In addition, we can use the expression for the period to explain why the number of clusters N_c arising in the network (1), when compared to the adaptation time constant ϵ_a, will scale as $N_c \propto \epsilon^{2/}$

formulae can be utilized extensively in the explanation of network dynamics.

In deriving our approximation to the periodic solution, we were able to calculate a relatively concise formula relating the period of the solution to the remainder of the parameters

$$T \approx \epsilon_a \ln\left[\frac{}{I} + 1\right] + \frac{\epsilon_a^{1/3}\epsilon_b}{+I}, \qquad (4)$$

where ϵ_b is the minimal solution to

$$\sqrt{3}\mathrm{Ai}(-B_{\epsilon_b}) = -\mathrm{Bi}(-B_{\epsilon_b}), \qquad (5)$$

such that $\epsilon_b > 0$ (see Text S1). We illustrate the accuracy of this approximation over a wide range of adaptation time constants ϵ_a in Fig. 5. The approximation is fairly accurate for a substantial region of parameter space, but improves appreciably as ϵ_a and are increased.

We conclude our study of the periodic solution to (2) by using our formula for the period (4) to roughly calculate the number of clusters admitted by a network of adapting neurons with pulsatile inhibitory coupling. This also provides us with an estimate of the population spike frequency. Any inputs delivered to the neuron during the initial or the outer layer stage of the solution, equation

are also nonlinear relationships derived here between cluster number and other parameters. We shall compare this formula further with the predictions we calculate using weak coupling and the phase-resetting curve. Since the perturbative solution ceases its slow dynamics briefly before the numerical solution (see Fig. 4), we expect that this asymptotic formula (6) approximating cluster size may be a slight underestimate.

Nonetheless, it allows us to concisely approximate how the population frequency depends on the adaptation time constant ϵ_a as well as the cluster number N_c. Since each neuron spikes with a period T given by equation (4) and there are N_c clusters of such neurons, the frequency of populations spikes in the network are given by

$$f_p = \frac{N_c}{T} = \frac{1}{\epsilon b \epsilon a^{1/3}}. \qquad \text{ð7Þ}$$

We plot this function versus ϵ_a as well as N_c in Fig. 6. Notice, networks with neurons whose spike frequency adaptation have a longer time constant support synchronous spiking rhythms with lower frequencies, as in the Traub network (see Fig. 1). Also, by our mechanism, as more clusters are added, the population frequency decreases. This is due to the period of individual neuron spiking scaling more steeply with adaptation time constant than the cluster number.

We have identified general relationships between the adaptation time constant and two quantities of the idealized spiking network (1): the period of a single neuron and the cluster number of the network. These relationships help characterize the behavior of the cluster state in the adaptive network. In particular, the bifurcation structure of the fast-slow formulation of the single neuron system guides the identification of a $\epsilon_a^{1/3}$ timescale of the spike phase, which evidently guides network level dynamics. Singular perturbation theory is indispensable in making this observation.

Phase-resetting curve of an adapting neuron

As a means of studying the susceptibility of a single neuron to synchronizing to input from the network, we shall derive the phase-resetting curve of a neuron with adaptation. Biophysically, the phase-resetting curve corresponds to the amount that brief inputs to a tonically spiking neuron delay or advance the time of the next spike. First, we make a change of variables $x = \tan(\theta/2)$ to the system (2), so the state of the neuron is now described by the quadratic integrate and fire (QIF) model with adaptation [58]

$$\dot{x} = x^2 + I - z,$$
$$\dot{z} = -z/\epsilon_a + (1/$$

Upon plugging this into (20), we find the eigenvalue associated with the nth mode of , is related to the Fourier coefficients a_m,b_m of H by

$$, _n = -Dn^2 - \frac{n\ _w b_n}{2} + in\left(\quad +2, \ _w a_0 - \frac{_w a_n}{2}\right). \qquad \text{ð22Þ}$$

Thus, as D is reduced towards zero, the first eigenmode to destabilize will be the one whose eigenvalue crosses from the left to the right half of the complex plane first. Using equation (22), we can identify this mode as the first n to have Re$_{\ n}=0$ or

$$\frac{2D}{_w} = -\frac{b_n}{n}.$$

This corresponds to the n for which $-b_n/n$ is maximal. For the critical D value at which the first eigenvalue has positive real part, we show plots of $, _n$ as a function of n for several different parameters in Fig. 9. Notice that as the adaptation time constant $_a$ is increased, and other parameters are held fixed, the critical n increases. As the synaptic time constant $_s$ is increased and other parameters are held fixed, the critical n decreases. We contrast this with the case of excitatory coupling (<0) in the system (1), where the PRC is nonnegative. In this case, the critical n is fairly insensitive to changes in the time constants, virtually always predicting the $n=1$ mode becomes unstable first (not shown). Therefore, our weak coupling calculation approximates the number of clusters N_c for a given set of parameters using the coupling function (17) with the Fourier expansion (21) so that

$$N_c = \mathrm{argmax}_{n\in Z+}\left(-\frac{b_n}{n}\right). \qquad \text{ð23Þ}$$

To compare with our singular perturbation theory results, we compute the approximate number of clusters using the weak coupling assumption for pulsatile synapses. In the limit $_s\to 0$, the coupling function becomes $H(\ )=-g(\ $

cluster number that accounts for synaptic timescale might include an inverse dependence upon τ_s.

Comparing numerical simulations to theoretical predictions of clustering

32. Sanchez-Vives MV, Nowak LG, McCormick DA (2000) Cellular mechanisms of long-lasting adaptation in visual cortical neurons in vitro. J Neurosci 20: 4286–99.
33. Tateno T, Harsch A, Robinson HPC (2004) Threshold firing frequency-current relationships of neurons in rat somatosensory cortex: type 1 and type 2 dynamics. J Neurophysiol 92: 2283–94.
34. González-Burgos G, Krimer LS, Urban NN, Barrionuevo G, Lewis DA (2004) Synaptic efficacy during repetitive activation of excitatory inputs in primate dorsolateral prefrontal cortex. Cereb Cortex 14: 530–42.
35. Buhl EH, Tama

they will evolve along a manifold determined by the slow subsystem

$$0 = 1 - \cos\theta + (1 + \cos\theta)(I - \beta z_0 e^{-s}), \tag{6}$$

where $s = \epsilon t$ is a slow time variable. We can solve (6) for the outer layer's dynamics

$$\theta(s) = -\cos^{-1}\left(\frac{I - \beta z_0 e^{-s} + 1}{\beta z_0 e^{-s} + 1 - I}\right). \tag{7}$$

Notice that this solution will vanish when $\beta z_0 e^{-\epsilon T_{SN}} = I$. This is related to the fact that as the total input to the neuron passes through zero, there is a saddle-node bifurcation in the equilibria structure of the associated fast subsystem [1]. This is a common mechanism for initiating the fast part of a relaxation oscillation [2]. The slow solution will therefore last about

$$T_{SN} = \frac{1}{\epsilon}\ln\frac{\beta z_0}{I}.$$

When the system reaches the vicinity of the saddle-node ($t \approx T_{SN}$), it will begin to evolve according to fast dynamics. Therefore, we must calculate the terminal dynamics of the periodic solution within a boundary layer. To do this, we presume perturbative solutions and fast timescales with arbitrary scaling $\theta = \epsilon^p\theta_1$ and $\tau = \epsilon^q(t - T_{SN})$. Substituting these expressions into (3), we have

$$\epsilon^{p+q}\frac{d\theta_1}{d\tau} = \frac{1}{2}\epsilon^{2p}\theta_1^2 + 2\beta z_0 e^{-\epsilon T_{SN}}\epsilon^{1-q}\tau.$$

Upon setting $p = q = 1/3$, we find the order of all terms is matched. Now, we apply the Riccati transformation $\theta_1 = -2\dot{y}/y$, as well as a change of variables $r = B\tau$, where

$$B = \left(\frac{\beta z_0 e^{-\epsilon T_{SN}}}{2}\right)^{1/3} = \left(\frac{I}{2}\right)^{1/3}.$$

This yields Airy's equation

$$\frac{d^2y}{dr^2} = ry,$$

which has general solutions

$$y(r) = c_1\mathrm{Ai}(r) + c_2\mathrm{Bi}(r),$$

Tf(B)TJEBT)0.96326264264A1(r) and Bi(r) are the Airy functions ... [illegible]

Substituting (9) into (2) and requiring self-consistency, we can solve for the initial condtion

$$z_0 = 1 + \frac{I}{\beta} e^{-\tau_d/\tau_b}.$$

Therefore, the time it takes to reach the saddle-node is

$$\begin{aligned} T &= \frac{1}{\alpha} \ln\left[\frac{\beta}{I} + e^{-\tau_d/\tau_b}\right] \\ &\approx \frac{1}{\alpha}\left[\ln\left(\frac{\beta}{I} + 1\right) - \frac{\alpha^2 \tau_d}{\beta/I + 1}\right], \end{aligned} \tag{10}$$

when we Taylor expand to first order. Plugging (10) into (9) and rewriting $\tau = 1/\alpha$, we have the approximation for the period of the solution

$$T \approx \tau \left[\ln\left(\frac{\beta}{I} + 1\right) + \beta\tau^{-1}\right]$$

Note, we use here for comparison with our singular perturbation theory results. Our next step is to employ the transformation $x = -\dot{y}/y$ to convert the Riccati equation (12) to

$$\frac{d^2y}{dt^2} = [\beta e^{-} - I]y,$$