

Diverse Origins of Network Rhythms in Local Cortical Circuits

Miles A. Whittington, PhD,¹ Roger D. Traub, MD,²
and Nancy Kopell, PhD³

¹Institute of Neuroscience
The Medical School, University of Newcastle-upon-Tyne
Newcastle-upon-Tyne, United Kingdom

²Department of Physical Sciences, IBM T. J. Watson Research Center
Yorktown Heights, New York

³Center for Biodynamics
Department of Mathematics and Statistics, Boston University
Boston, Massachusetts

Introduction

Oscillatory electrical activity in populations of neurons is a near-ubiquitous feature of massively parallel brain regions such as the neocortex and cerebellum. It is also observable in subcortical structures such as the inferior olive, thalamic nucleus reticularis, striatum, and even the spinal cord. It has been argued that observation of brain rhythms is epiphenomenal—that methods for measuring electrical activity in populations of neurons requires local synchronization in order to generate a signal large enough to detect, e.g., using surface electroencephalography (EEG) electrodes. Because local synchrony is an intrinsic feature of neuronal population dynamics during rhythm generation, it is not surprising that these rhythms form a major component of the signals studied. However, population rhythms are observable at the level of multiple single-neuron unit recordings, and their causal connection with neuronal synchronization has been extensively studied and linked to many aspects of cognitive and motor function (Baker, 2007; Fries et al., 2007). The purpose of this chapter is not to review these links. Instead, we wish to take a reductionist path and try to understand how networks of neurons generate brain rhythms in the first place.

The Basic Building Blocks of Cortical Rhythms

Cortical rhythms are seen at many scales in the brain. Macroscopic recordings using surface EEG and magnetoencephalography (MEG) readily demonstrate dynamic interactions at the whole brain level. The spatial scale of these interactions has been correlated with the actual frequency of rhythm observed (von Stein and Sarnthein, 2000). However, *in vitro* slice preparations have taught us that the entire range of the EEG/MEG spectrum in whole brain *in vivo* recordings (from fractions of 1 Hz up to many hundreds of Hz) can be reproduced in tissue volumes $<1 \text{ mm}^3$. Furthermore, *in vivo* observations showing the existence of discrete classes of cortical rhythm within the EEG spectrum can be replicated with even greater temporal precision in small sections of isolated neocortex (Draguhn and Buzsáki, 2004; Roopun et al., 2008). At even smaller scales, rhythms are seen in simple neuronal networks within single laminae in neocortical slices, and resonance is seen in single neurons and even within individual neuronal compartments. It is clear then that cortical rhythms both manifest, and have their origins, across a very broad range of spatial and network scales. We will briefly consider some of the key rhythm-generating mechanisms at work at various scales within oscillating networks.

Intrinsic properties

Individual neurons often show subthreshold membrane potential oscillations. Interactions between subthreshold and threshold rhythms lead to input and output frequency preferences that can vary dramatically across different cell compartments. For example, the main neocortical neuronal cell type, the regular spiking (RS) cell, demonstrates a rich set of intrinsic dynamics based purely on the type and compartmental localization of intrinsic conductances (Traub et al., 2003a). Out in apical dendrites, a combination of sodium, potassium, and calcium conductances induces coexistent gamma (40 Hz) and theta (~ 6 Hz) rhythms on tonic depolarization. In contrast, combinations of persistent sodium and BK potassium channels in somata induce a use-dependent transition between regular spiking at ~ 10 Hz (alpha EEG frequency) and repetitive, brief burst generation at ~ 20 Hz (beta EEG frequency). All this can readily occur in the absence of any synaptic or gap junctional connectivity with other neurons. In other words, to understand the network manifestation of these rhythms, it is vital that we understand how such neuron compartment-specific intrinsic properties interact with patterns of neuronal connectivity.

Gap junctions

The simplest, phylogenetically and developmentally oldest form of neuronal intercommunication is via gap junctions. Hexameric assemblies of certain connexin/pannexin proteins form pores in cell membranes that, when paired with pores in adjacent cell membranes, form a conduit between cells passable by small molecules and ions. Gap junctions are formed by plaques of many of these pores, giving an effective way for one neuron to “share” membrane potential changes with neighbors, but they are far from being just “holes” in membranes. Different gap junctions have different electrical properties; these include rectification and low-pass filtering depending on connexin composition and compartmental localization. Gap junctions’ conductance state is also exquisitely modulated by second messenger systems, neuronal metabolic state, and pH. Low-pass filtering gap junctions are prominent between somatodendritic compartments of fast-spiking interneurons, with somata ~ 50 – 200 microns apart. Although gap junctions do not take part in rhythm generation per se in networks of these interneurons, they do help stabilize gamma frequency dynamic properties in such networks (Traub et al., 2003b). In contrast, gap junctions between axonal compartments of excitatory projection neurons (also with somata less than a few 100 microns of each other) do not act as low-pass filters and can reliably transmit very fast frequency events (Schmitz et al.,

NOTES

2001). Much of this aspect of gap junctions' role in network rhythms will be dealt with in R. Traub's chapter (Modeling Rhythms: Detailed Cellular Mechanisms of *In Vitro* Oscillations with Emphasis on Very Fast Oscillations). However, we will revisit it here when considering how gap junctional communication between neurons is influenced by the intrinsic properties of these neurons.

Synaptic inhibition

At the next level of the network spatial scale, we must consider synaptic inhibition. Local circuit inhibitory neuronal axons can extend 1 mm or more, effectively giving them the ability to coordinate rhythms in networks approximately one order of magnitude larger than local circuit connections using gap junctions (above). It should be noted that some synaptic inhibition can originate from principal, projection neurons over much greater spatial scales (e.g., cerebellar Purkinje cells), but they will not be dealt with here. Synaptic inhibition, particularly mediated by GABA_A receptors, is a prime cause of rhythm generation in local networks for frequencies ranging from theta to gamma (~4–80 Hz). Local circuit interneurons are readily induced to fire even by extremely low levels of excitatory neuronal activity; they have resting membrane potentials close to their firing thresholds and rapid after-hyperpolarizing kinetics, which facilitate high spike frequencies.

The important role of inhibitory interneurons in coordinating networks is demonstrated by the enormous degree of convergence of inputs and divergence of outputs for individual interneurons. One fast-spiking interneuron receives synaptic inputs from as many as 1500 principal cells and, in turn, can provide inhibition back to up to 500 of these neurons. In addition, these interneurons inhibit each other and are gap-junctionally coupled. This immense degree of interconnectivity in local neuronal networks gives a powerful means of generating network rhythms to sense and control principal cell-spike timing with high spatiotemporal precision.

With such rhythms, the frequency is set, for the most part, by the kinetics of the IPSPs onto target neurons. Kinetics, in turn, depends on the interneuron subtype and, more importantly, the compartmental location of the inhibitory synapse on the target neuron. For fast-spiking interneurons with perisomatic principal cell targets, fast postsynaptic GABAergic inhibitory events lead to local population rhythms from a frequency of ~30 Hz up to ~80 Hz (Traub et al., 1996). In contrast, distal dendrite-targeting interneurons (although also capable of fast spiking)

generate postsynaptic inhibitory events with much slower kinetics (Banks et al., 2000). Such inhibitory events combine with intrinsic conductances in dendrites (discussed above) to generate robust local-circuit theta rhythms in networks.

Synaptic excitation

In cortex, excitatory synapses recruit a proportion of principal neurons, and all interneurons, into local network rhythms. In addition, excitatory projection neurons send out collaterals as far as 5 mm horizontally in neocortex; primary axonal projections can extend as far as 10 cm or more in human brain (e.g., the parietofrontal projection). Although it is theoretically possible for such connections to generate local rhythms, we need to consider the relative occurrence and properties of excitation onto other principal cells and onto interneurons.

Excitatory local circuit synapses onto interneurons are common (see above) and have a number of properties which make them ideal for recruiting these cells. Glutamatergic synapses onto interneurons have a high probability of transmitter release and very low failure rates. Individual synapses generate large unitary postsynaptic events with very rapid kinetics. Taken together, these properties provide a reliable and potent way for even single principal cell action potentials to induce firing in local interneurons (Traub and Miles, 1995). In addition, excitatory synapses onto some fast-spiking interneurons show anti-Hebbian plasticity, suggesting that excitatory synaptic strength onto interneurons increases for silent interneurons until spiking is actually generated (Lamsa et al., 2007). In stark contrast, local circuit synaptic excitation onto other excitatory neurons is rather sparse. Estimates from paired recordings give probabilities of finding coupled principal cell pairs (within a single lamina) from 1:100 to ~1:30 (Deuchars and Thomson, 1996; Thomson and Deuchars, 1997). In addition, excitatory synapses onto excitatory cells demonstrate a relatively low release probability, high failure rates, and slower kinetics. Coupled with normal Hebbian plasticity (which implies that postsynaptic neurons must already be capable of generating spikes for a given input before potentiation can take place), these sparse recurrent excitatory connections would be expected to play only a minor role in generating local circuit rhythm. However, these properties do favor transmission via burst discharges (bursting being a neuronal property dictated by intrinsic properties such as m-current density and calcium-channel activation) and may underlie bistable membrane potential transitions through temporal summation of slow postsynaptic events (see the third example, below).

Piecing Together Interneuronal Communication

Even in a region of cortex as small as one column, a multitude of neuronal subtypes exist. At least seven different types of excitatory neuron and more than a dozen subtypes of inhibitory interneuron have been identified: Each has its own complement of intrinsic properties imparting compartment-specific preferred frequencies of input selection and output generation. Couple this fact with the array of available mechanisms for interneuronal communication, and it is hardly surprising that the brain can generate rhythms over a broad range of temporal and spatial scales. Next, we give three specific examples of how different interneuronal communication strategies and intrinsic properties can combine to generate different rhythms. In addition, we give an example of how different mechanisms underlying the same frequency of population rhythm—far from complicating our understanding of rhythm generation—can aid our understanding of how different local subnetworks can combine to produce robust interactions across different frequency bands.

An example of rhythms generated by gap junctions and intrinsic neuronal conductances

In the lateral ventricle (LV) of neocortex, intrinsically bursting (IB) neurons, during depolarization, generate weak beta-frequency (~25 Hz) resonance as a consequence of interaction between active and passive conductances in axonal compartments (Roopun et al., 2006). At the single-cell level, brief axonal burst discharges can be generated by fast sodium and potassium conductances. During external drive to the axon, multiple bursts can be seen separated by a quiescent period whose duration is set by the magnitude of m-current within axons. This single-neuron beta2 resonance is also manifest as a population rhythm within the association cortex of rodents, but is not sensitive to the blockade of GABA or glutamate receptor-mediated synaptic communication between neurons. The population rhythm is, however, abolished by gap-junction blockade with carbenoxolone. This property, coupled with the existence of sharp partial spikes in somatic recordings, suggests that the manifestation of this cellular rhythm within networks is entirely mediated by gap-junction communication by the active compartments of IB neurons (Fig. 1).

Here is an example of a population rhythm occurring in a network consisting of a single neuron subtype without conventional chemical synapses. Not only are the intrinsic conductances in each cell acting to

tune the periodicity directly manifest in the local field potential, but there is genuine synergism between the intrinsic axonal resonance and the mode of connectivity. Axonal spike rates are potentiated by axo-axonic gap-junction communication, thereby boosting the excitation to axons, increasing the beta rhythm power observable in individual cells, and synchronizing the beta rhythm across many thousands of IB cells. These effects demonstrate that, in some circumstances, it may be entirely insufficient to model cortical activity on the basis of single compartment neurons and classical chemical neurotransmission.

An example of rhythms generated by recurrent synaptic excitation and intrinsic neuronal conductances

The slow wave oscillation (<1 Hz) associated with deep sleep is another example of how attempting

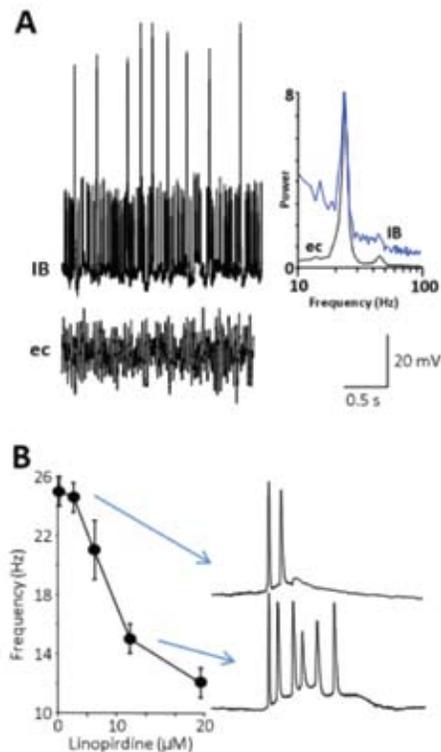


Figure 1. Beta2 rhythm generation in a population of IB neurons connected only by axo-axonic gap junctions. **A**, Concurrent somatic IB cell and LV field potential recording showing preponderance for partial spikes in soma. Both intracellular and extracellular recording show the beta2 rhythm. **B**, This beta rhythm is modified by changing intrinsic properties of the IB cell axon. Reduced m-current with the drug linopirdine increases individual neuronal burst duration (examples shown) and slows population frequency (data plotted in the graph).

NOTES

to understand rhythm generation using chemical synaptic connections alone may be insufficient for explaining cortical dynamics. In entorhinal cortex, a sparse pyramidal neuronal network enables signaling between cells mediated by slow glutamate receptors (GluR5-mediated kainate responses). Postsynaptic events using this communication strategy have kinetics on the order of many tens of milliseconds. Although unitary events are small, the temporal window for summation is broad, and even low levels of “random” activity in such a recurrent excitatory network generate large, stable depolarizations via positive feedback (Frerking and Ohliger-Frerking, 2002). This network mechanism is sufficient to produce “up-states” associated with the active part of each slow wave period, but what then produces a return to a “down state” and completes the cycle?

In the example in Figure 2, the active, “up-state” generates action potentials at a rate that depletes each neuron’s store of energy in the form of ATP. As ATP levels fall, block of intrinsic conductance mediated by ATP-sensitive potassium channels (Kir 6 family) diminishes, potassium conductance increases, and neuronal membrane hyperpolarization follows. The network then remains quiescent until energy levels are restored, background activity reaches the threshold required for temporal summation of synaptic excitation, and the next “up-state” is generated. This thresholding effect of background network activity on EPSP summation (and the threshold effect for termination of the “up-state”) generates a rhythm that is more bistable than sinusoidal (Cunningham et al., 2006). In addition, for this process to occur, the metabolic state of the network must be low. If neuronal metabolism is high, then ATP production rates are sufficient to support continued activity (a persistent “up-state”) and the rhythm is abolished. Thus, when considering the mechanisms that generate a network rhythm, we must also consider the metabolic state of the neurons involved.

An example of rhythms generated by synaptic inhibition and intrinsic neuronal conductance

The above two examples show how rhythms vastly different in frequency can be generated within networks consisting of only one type of neuron using a single complement of intrinsic conductances and one type of interneuronal communication. However, even simple local circuits are much more heterogeneous than this. We will now consider a situation in which such heterogeneity in cell type, interneuronal

communication, and intrinsic properties works synergistically to generate a population oscillation. As mentioned above, interneuron subtypes are very diverse, as are the kinetics of inhibitory synaptic events they produce. In hippocampus, one form of theta-frequency local rhythm (~6–12 Hz) involves both dendrite targeting (slow inhibition-generating) and perisomatic targeting (fast inhibition-generating) fast-spiking interneurons. The former, oriens-lacunosum moleculare (O-LM) cells, contains intrinsic conductances including the hyperpolarization-activated current I_h , which makes them weakly resonant at theta frequencies on tonic depolarization. The latter (basket cells) shows no such resonance and readily generates trains of spikes at many hundreds of Hz. The weak theta resonance of O-LM cells is insufficient to support a theta-frequency population rhythm alone, but the interaction between these two types of interneuron certainly is (Rotstein et al., 2005).

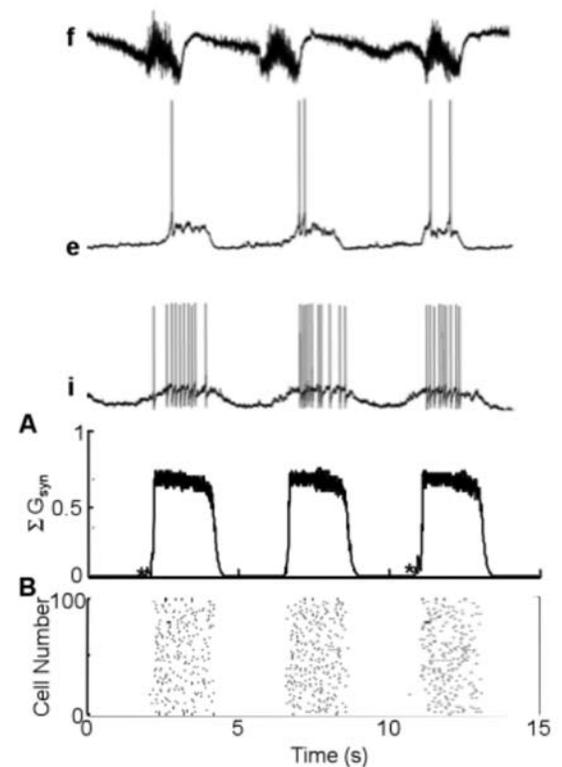


Figure 2. Slow wave oscillations (up-down states) induced by kainate receptor-mediated recurrent excitation and $g_{K_{ATP}}$. Rhythmic epochs of activity in field potential (f) are accompanied by “up-states” in pyramidal (e) and inhibitory (i) neurons. **A**, A model of pyramidal cells recurrently connected by kainate receptor-mediated synaptic excitation generates such up-down state transitions when neuronal activity is coupled to metabolic state. **B**, Action potential generation feeding into $g_{K_{ATP}}$ activity.

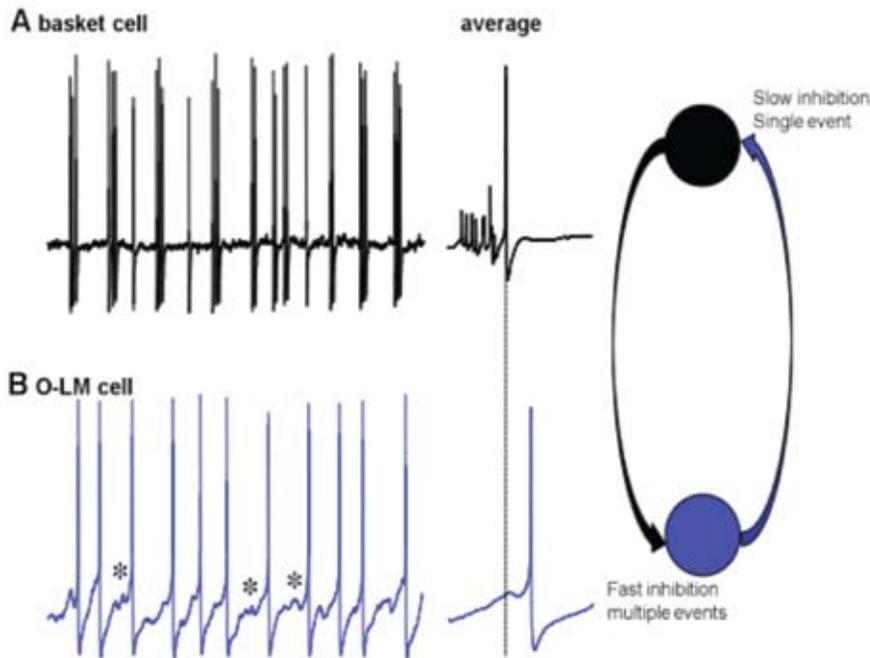


Figure 3. Theta rhythms in heterogeneous interneuronal networks connected by slow and fast inhibition. **A**, During population, theta oscillations basket cells fire brief bursts of spikes terminated by slow hyperpolarization (revealed in the terminal spike-triggered average) presumed to come from the synaptic input of O-LM cells. **B**, During the same theta rhythm, O-LM cells fire single spikes on each period; spike timing corresponds to the termination of each basket-cell burst. Before each O-LM spike, runs of fast inhibitory synaptic potentials are seen in the raw trace and in the spike-triggered average.

The key mechanistic features of the O-LM–basket cell local circuit underlying theta generation are as follows:

- (1) O-LM neurons generate single spikes at theta frequency;
- (2) Following a single O-LM spike, basket cells receive an apparent slow IPSP, which terminates their fast-spiking output;
- (3) As this inhibitory synaptic event decays, fast spiking resumes in basket cells; and
- (4) The resulting fast IPSPs received by O-LM cells serve to rapidly and repetitively activate I_h until membrane potential breaks free from this inhibitory barrage and the next O-LM spike is generated (Fig. 3).

To generate a theta rhythm with such an interaction, the heterogeneity of inhibitory synaptic kinetics is vital, as is the heterogeneity in I_h distribution across the two cell types.

Implications from cross-frequency interactions

For the above example of theta generation, why do we need such a complex mechanism for a simple rhythm? One aspect of this mechanism is that inherent in the

emergent network's behavior is the ability to “nest” higher frequency rhythms (e.g., gamma, 30–80 Hz) mediated by basket cells within the theta rhythm. Amplitude modulation of gamma rhythms by coexpressed theta oscillations is a common feature of hippocampal population rhythms during exploration (Chrobak et al., 2000). We are also beginning to understand how other forms of cross-frequency interaction may be generated by heterogeneity in neuronal subtype and interneuronal communication. The final, and most complex, example of rhythm generation involves interaction between laminae in neocortex. Both gamma rhythms (~40 Hz) and beta2 rhythms (~25 Hz) are seen in superficial and deep cortical laminae, respectively (Roopun et al., 2006). However, a reduction in tonic excitation to cortex results in these two rhythms combining through period concatenation to generate a third rhythm: beta1 (~15 Hz) (Roopun et al., 2008).

The resulting rhythm requires two subtypes of principal cell (layer 5 IB cells, discussed above, and superficial RS cells) and two subtypes of interneuron (fast spiking and low threshold spiking [LTS]). The reduced excitation to cortex serves to ensure that

NOTES

principal-cell spikes are generated through rebound excitation alone, mediated by activation of the intrinsic conductance I_h (Kramer et al., 2008). For rebound spiking to occur, the two interneurons must still be active in order to provide the hyperpolarization required to bring the membrane potential of principal cells down to levels where I_h can participate in rebound depolarizations.

The basic sequence of concatenation is as follows:

- (1) Burst firing in layer 5 IB cells activates superficial fast-spiking interneurons;
- (2) These interneurons provide a brief IPSP to superficial RS cells (as they would during the earlier gamma rhythm), inducing a rebound action potential thereafter;
- (3) This superficial principal cell output is sufficient to activate the second interneuron subtype involved: LTS cells; and
- (4) Output from these interneurons targets dendrites of principal cells, producing a slower IPSP, which causes rebound spiking approximately one beta2 period later (Fig. 4).

Summary

The diversity of frequency preferences that intrinsic conductances impart, compounded by the array of neuronal communication strategies and their accompanying kinetics, provides for a broad range of rhythm generation in small regions of cortex.

Therefore, to understand even the most basic dynamic features of local circuits, it is necessary to take a reductionist approach to capturing the salient mechanisms experimentally at multiple scales. One's purview must take in everything from conductances in single neuronal compartments, to the target specificity and kinetics of synaptic and nonsynaptic neuronal communication, to the effects of global variables such as neuromodulatory and metabolic states. Although elegant "reduced" models can tell us much about the dynamics of specific rhythms, only by incorporating all these observations to generate biologically realistic computational models can we hope to understand the role that time plays in cortical information processing.

References

- Baker SN (2007) Oscillatory interactions between sensorimotor cortex and periphery. *Curr Opin Neurobiol* 17:649-655.
- Banks MI, White JA, Pearce RA (2000) Interactions between distinct GABA(A) circuits in hippocampus. *Neuron* 25:449-457.
- Buzsáki G, Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304:1926-1929.
- Chrobak JJ, Lorincz A, Buzsáki G (2000) Physiological patterns in the hippocampo-entorhinal cortex system. *Hippocampus* 10:457-465.

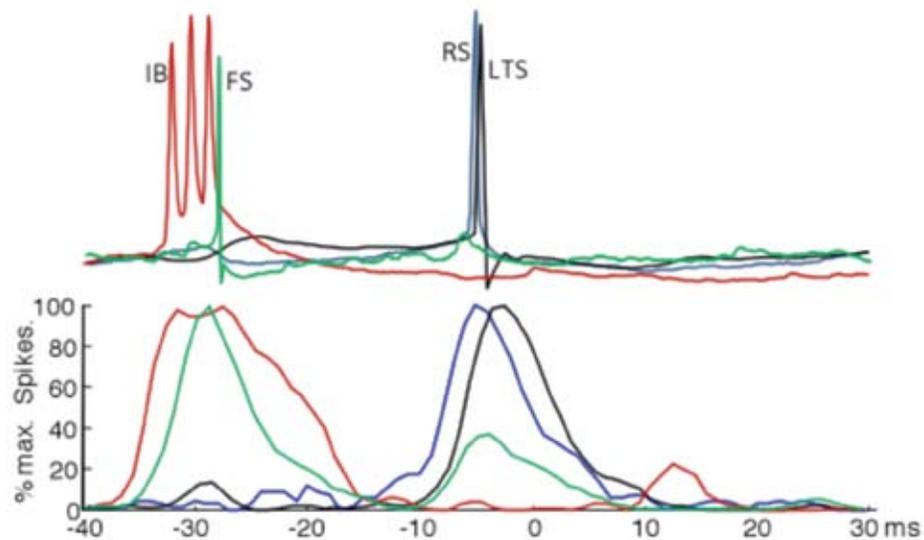


Figure 4. The sequence of spiking in four cortical neuron subtypes during beta1 rhythms generated by concatenation of gamma and beta2 rhythms. Single examples of spiking in one beta1 period are shown for each cell (top), each aligned to the concurrently recorded beta1 field potential (not shown). Average firing probabilities (bottom graph) demonstrate the sequence of spiking with one gamma period separating deep-layer principal neuronal firing and superficial-layer principal neuronal firing. IB = LV intrinsic bursting neuron; FS = fast-spiking interneuron; RS = superficial layer regular spiking neuron; LTS = superficial layer low-threshold spiking neuron.

- Cunningham MO, Pervouchine DD, Racca C, Kopell NJ, Davies CH, Jones RS, Traub RD, Whittington MA (2006) Neuronal metabolism governs cortical network response state. *Proc Natl Acad Sci USA* 103:5597-5601.
- Deuchars J, Thomson AM (1996) CA1 pyramidal connections in rat hippocampus *in vitro*: dual intracellular recordings with biocytin filling. *Neuroscience* 74:1009-1018.
- Frerking M, Ohliger-Frerking P (2002) AMPA receptors and Kainate receptors code different features of afferent activity. *J Neurosci* 22:7434-7443.
- Fries P, NiKolic D, Singer W (2007) The gamma cycle. *Trends Neurosci* 30:309-316.
- Kramer MA, Roopun AK, Carracedo LM, Traub RD, Whittington MA, Kopell NJ (2008) Rhythm generation through period concatenation in rat somatosensory cortex. *PLoS Comput Biol* 5;4(9):e1000169.
- Lamsa KP, Heeroma JH, Somogyi P, Rusakov DA, Kullmann DM (2007) Anti-Hebbian long-term potentiation in the hippocampal feedback inhibitory circuit. *Science* 315:1262-1266.
- Roopun AK, Middleton SJ, Cunningham MO, LeBeau FE, Bibbig A, Whittington MA, Traub RD (2006) A beta2-frequency (20-30 Hz) oscillation in nonsynaptic networks of somatosensory cortex. *Proc Natl Acad Sci USA*. 103:15646-15650.
- Roopun AK, Kramer AK, Carracedo LM, Kaiser M, Davies CH, Traub RD, Kopell NJ, Whittington MA (2008) Temporal interactions between cortical rhythms. *Front Neurosci* 2:145-154.
- Rotstein HG, Pervouchine DD, Acker CD, Gillies MJ, White JA, Buhl EH, Whittington MA, Kopell N (2005) Slow and fast inhibition and an h-current interact to create a theta rhythm in a model of CA1 interneuron network. *J Neurophysiol* 94:1509-1518.
- Schmitz D, Schuchmann S, Fisahn A, Draguhn A, Buhl EH, Petrasch-Parwez E, Dermietzel R, Heinemann U, Traub RD (2001) Axo-axonal coupling: a novel mechanism for ultrafast neuronal communication. *Neuron* 31:831-840.
- Thomson AM, Deuchars J (1997) Synaptic interactions in neocortical local circuits: dual intracellular recordings *in vitro*. *Cereb Cortex* 7:510-522.
- Traub RD, Miles R (1995) Pyramidal cell-to-inhibitory cell spike transduction explicable by active dendritic conductances in inhibitory cell. *J Comput Neurosci* 2:291-298.
- Traub RD, Whittington MA, Stanford IM, Jefferys JG (1996) A mechanism for generation of long-range synchronous fast oscillations in the cortex. *Nature* 383:621-624.
- Traub RD, Buhl EH, Gloveli T, Whittington MA (2003a) Fast rhythmic bursting can be induced in layer 2/3 cortical neurons by enhancing persistent Na⁺ conductance or by blocking BK channels. *J Neurophysiol* 89:909-921.
- Traub RD, Pais I, Bibbig A, LeBeau FE, Buhl EH, Hormuzdi SG, Monyer H, Whittington MA (2003b) Contrasting roles of axonal (pyramidal cell) and dendritic (interneuron) electrical coupling in the generation of neuronal network oscillations. *Proc Natl Acad Sci USA* 100:1370-1374.
- von Stein A, Sarnthein J (2000) Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *Int J Psychophysiol* 38:301-313.