Modeling Rhythms: from Physiology to Function

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Introduction

The central issues of this course are the roles that neocortical rhythms play in health and sickness. This and the previous chapter, by R. Traub and M. Whittington, deal with computational modeling, but from different perspectives. Although much of Roger Traub's work has been devoted to very detailed models of biophysical phenomena, some of the work he is describing in this course, and the work in this chapter, can be considered "reduced"; that is, it focuses on specific aspects of the extraordinary complexity of neural circuits that give rise to brain rhythms. In the previous chapter, the main aim was to understand the origins of very fast oscillations (VFOs). The authors made the case that the centrally important details concern network topology and that the physiological underpinnings of the dynamics have less importance. This chapter aims to connect mechanisms of lower frequency rhythms with functions of brain rhythms. Here the properties of the intrinsic and synaptic currents turn out to be the heart of the story, with the anatomy playing a much smaller role.

I focus here on "cell assemblies," a phrase that denotes collections of neurons that fire in approximate synchrony for a short period of time, whether or not these cells have direct synaptic connections. About 20 years ago, W. Singer and C. Gray presented data suggesting that the gamma oscillation is related to the binding of different kinds of input in early sensory processing (Gray et al., 1989; Singer and Gray, 1995). Since then, a burgeoning literature has appeared that discusses the association of brain rhythms with various tasks and the biophysical underpinnings of the various kinds of brain rhythms. Thus, it is timely to reconsider how brain rhythms (considered more broadly than just the gamma rhythm) can participate in "binding," that is, the creation, protection, and interaction of cell assemblies. Modeling plays an essential role in this reconsideration by focusing attention on those properties of brain circuitry and physiology that are most important for issues of binding.

Brain Rhythms and Mechanisms

Brain rhythms cannot be completely characterized by their frequencies, nor can any given function be mapped to a single frequency (see the chapter by C. Tallon-Baudry, Rhythms in Cognitive Processing). The classical frequency ranges delta (1–4 Hz), theta (4–8 Hz), alpha (9–11 Hz), beta1 (12–18 Hz), beta2 (19–30 Hz), and gamma (30–90 Hz) were taken from EEG studies of human patients in various experimental paradigms; as such, they were associated with topography and behavior as well as frequency. For example, the classical alpha rhythm is found in the posterior part of the brain when the subject has eyes closed. Now that many more ways are available to probe for rhythms in animal as well as human subjects, the boundaries among frequency bands has blurred, creating confusion about what should be considered "different" rhythms.

I suggest that a better way to distinguish among rhythms is to consider the dynamical mechanisms underlying any given oscillatory pattern. (Later on, I will give examples of what I mean by "dynamical mechanism.") In different animals, or even within different brain structures, the same mechanism can correspond to diverse frequencies. Further, the same frequency rhythms may be produced by multiple mechanisms. Mechanisms give important clues to function, allowing us to see why different rhythms may be used for different functions. The physiology associated with the different dynamical mechanisms is taken largely from *in vitro* work (as discussed in the chapter by M. Whittington, Diverse Origins of Network Rhythms in Cortical Local Circuits). However, what is known about *in vivo* rhythms is completely consistent (Atallah and Scanziani, 2009; Cardin et al., 2009). The computational modeling bridges the data we have from the *in vitro* models with the behavioral data from *in vivo* models.

Excitation, Inhibition, and Synchronization at Gamma Frequencies

Because the formation of cell assemblies involves synchronization of neurons, the latter is a good place to start. Both excitation and inhibition can give rise to synchronization, though in different ways. A large pulse of excitation resets cell spiking by causing the cells to spike almost immediately. Counterintuitively, however, it is inhibition that is more effective, especially in the context of noisy inputs. The inhibition hyperpolarizes or shunts inputs for a relatively fixed period that depends on the baseline excitability of the cell and the size of the IPSPs, determining the time until the next spikes (Ermentrout and Kopell, 1998). Noisy inputs have much less effect than they would have had if the synchronization were by excitation. This effect of common inhibition is likely the basis of "phase resetting," which is seen when excitation triggers a pulse of inhibition (Talei Franzesi et al., 2009).

All the network-based versions of the gamma rhythm appear to depend on this property of common inhibition (Whittington et al., 2000). I will discuss

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only those for which excitation plays an important role, since these are the ones most relevant to cell assemblies. Pyramidal interneuronal network gamma (PING) is induced *in vitro* by tetanic stimulation of hippocampal slices. In PING, the stimulation is higher frequency than gamma; when the stimulation is over, the network keeps firing at a gamma frequency for a short time. During this brief period, the excitatory pyramidal cells fire on each cycle, as do the inhibitory fast-spiking interneurons (Whittington et al., 2000). Although this gamma frequency was produced in the hippocampus, it is believed that the essential elements are the same in neocortex.

In its most basic incarnation, PING is a simple interaction of an excitatory cell (pyramidal) and an inhibitory cell (fast-firing interneuron, e.g., basket cell). We refer to these as "E-cells" and "I-cells." The excitation from the pyramid causes the I-cells to spike, which inhibits both cells, and the cycle begins again when the inhibition wears off. The only currents other than synaptic ones that are important here are the standard spiking currents. This is partly because the high-voltage regime in which gamma rhythm occurs makes inhibition-induced currents such as I_h and I_T irrelevant, and because other currents are much smaller than the spiking and synaptic currents. This oscillation has also been studied in larger sparse, heterogeneous networks (Borgers and Kopell, 2003). The I-cells synchronize their target population, the E-cells; in turn, the E-cells synchronize the I-cells more crudely, but enough to add to the process.

Another kind of gamma rhythm is induced *in vitro*, not by tetanic stimulation but by bath application of kainate, a glutamatergic agonist, and/or carbachol, a cholinergic agonist. The result is a network state in which E-cells fire once in a while, rather noisily, but the rhythm is kept going by the I-cells, with the help of some E-cells during each cycle (Traub et al., 2005). This state can be achieved when there is a significant amount of noise in the system, the cells are relatively excitable, but there is no massive input to a subset of cells. A very similar state is achieved with acetylcholine in the bath. This kind of gamma rhythm has been modeled by R. Traub and colleagues, using axo-axonal gap junctions (see the previous chapter by Traub and Whittington). In the simpler model used in this chapter, the cells are one-compartment (no plexus), and the needed noise is described phenomenologically, rather than constructed from a more detailed network (Borgers et al., 2005). Some of us associate this state with a background attentional state, or a state of vigilance, whereas the PING state is associated with cell assemblies within this background state. Modeling has shown that activating a background rhythm allows smaller input to create cell assemblies (Borgers et al., 2005).

Gamma Oscillations and Cell Assemblies

Many researchers, starting with Wolf Singer, have related gamma rhythms to the formation of cell assemblies. Indeed, gamma oscillations appear prominently exactly at the time and place binding would be highly desirable, e.g., during early sensory processing. An understanding of the physiological origin of PING shows why gamma rhythmicity is perfectly suited to the creation of cell assemblies. E-cells with enough excitability to fire in a given cycle do so, activating the inhibitory cells, which then suppress the other E-cells. This sequence of events creates a cell assembly, which does not change as long as the input is the same. The essential reason is that the PING mechanism of gamma rhythmicity is tied to the decay time of inhibition, which is the longest time constant in the network during gamma oscillations. (Other subthreshold currents play a much smaller role in the high-voltage ranges associated with PING.) From cycle to cycle, there is no memory, and the same cells that are activated in one cycle remain activated as long as the input is the same (Olufsen et al., 2003).

Cell assemblies that are formed in this way compete with one another if they share interneurons, a property that is very useful for the involvement of gamma rhythms in attention (Borgers et al., 2005, 2008; Borgers and Kopell, 2008). If some stream of input is given to a subset of E-cells in a network displaying background gamma, then that set can form a cell assembly. If a somewhat larger input is subsequently given to another subset of E-cells, the firing of the first subset is suppressed. The competition takes place via the inhibitory cells that are shared in the network. Although such lateral inhibition can be done without rhythms, modeling work shows why gamma rhythms make this competition more efficient (Borgers et al., 2005).

Another way in which gamma oscillations create competition is by allowing individual cells to respond only to inputs that are highly coherent and locking out other inputs of similar amplitude that are less coherent. The reason for this selectivity comes, as before, from the fine timing of the inhibition within the target E-I network: The inputs from the "distractor" come when there is a significant amount of inhibition locked to the primary input, and the

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effects are shunted (Borgers and Kopell, 2008). The larger the distractor, the more inhibition is needed. This effect happens only when the inputs fall within the gamma frequency range, since the gamma band is tied to the decay time of inhibition. Each time the chosen E-cells fire, they create a bath of inhibition that lasts the length of the gamma cycle. Thus, gamma is excellent for creating cell assemblies that lock out competing cell assemblies that share fast-firing interneurons. However, this property makes the gamma rhythm less useful for situations in which it is important to "bind" multiple kinds of information.

The Dynamical Mechanisms of Somatosensory Beta1

To understand what other rhythms might be doing in the creation, protection, and interaction of cell assemblies, it is useful to look at the physiology underlying the rhythms. For the beta rhythm, I'm going to focus on the versions of the beta1 and beta2 frequency bands found in the rodent secondary somatosensory system (S2) (discussed in the chapter by M. Whittington, Diverse Origins of Network Rhythms in Cortical Local Circuits). S2 is particularly interesting because it is a parietal regime associated with multimodal interactions. Here, too, an understanding of the dynamical mechanisms underlying the rhythms helps to illuminate the functional properties of those rhythms.

As discussed by Whittington, the superficial layers of S2 produce a persistent gamma rhythm *in vitro*, with kainate in the bath. This is modeled as described earlier, though we also add other interneurons known to be found in the superficial layers, specifically, low-threshold spiking (LTS) neurons. These tend to be almost silent in the superficial mini-slices during gamma rhythm, but when input from the deep layers causes them to fire, they can interfere with gamma rhythm. The beta2 rhythm in the deep layers survives the blocking of all synaptic receptors, so it is not a network phenomenon like gamma (Roopun et al., 2006). Thus, the beta2 rhythm is essentially a single-cell phenomenon, with the gap junctions helping to coordinate the cells. The deep 25 Hz rhythm is bursty, and its period is governed by an M-current that builds up and shuts off the burst (Roopun et al., 2006; Kramer et al., 2008).

In the model, intrinsically bursting (IB) cells in the deep layers connect to both kinds of inhibitory cells; these are the ascending connections. The descending connections go from the LTS cells to the apical dendrites of the deep IB cells. The connections are weak enough to allow the two rhythms to coexist without much disturbance. The layers do disturb one another and, in both experiment and model, the power is somewhat attenuated when the two layers interact. The nonspiking currents in the various compartments play a more important role in the beta rhythms than in the gamma rhythms. This is especially true of the h-currents in the IB cell dendrites, the regular spiking (RS) neurons, and the LTS cells. Inhibition turns on these currents and encourages rebound bursting, which is critical for the beta1 rhythm as we understand it.

What causes the switch from superficial gamma/deep beta2 dynamics to beta1 dynamics in all the layers? We suggest that, during the fast gamma and beta2 of the oscillation, there is plasticity, increasing the recurrent excitatory connections of the deep IB cells. However, the plasticity by itself does not cause the switch, which also requires the later removal of the drive to cells. We model the removal of the kainate by hyperpolarizing axons and dendrites of IB cells, and all the superficial cells, because all these are known to be depolarized by kainate. The effect of the removal is to create a concatenation of gamma and beta2, and a disappearance of the individual rhythms (also discussed in the Whittington chapter). The burst of IB cells, now more coherent because of the plasticity, activates the superficial inhibitory cells. The E-cells fire on a rebound from this inhibition after about 25 ms. This causes the LTS cells to fire, which inhibits the dendrites, and the IB cells then fire from a rebound about 40 ms later. As in the experiments, the 40 ms period of the "beta2 portion" of the beta1 frequency is determined by dendritic dynamics of the IB cells rather than by the axonal dynamics for the deep layer beta2 when the slice was more activated. Although this sequence of events seems extremely complicated, the model and experiments have yielded matching conclusions (Kramer et al., 2008).

Beta1 Rhythms and Cell Assemblies

In vivo beta1 appears to be a rhythm that is displayed after the exciting stimulus is gone (Tallon-Baudry et al., 1999; Haenschel et al., 2000). The physiology associated with the *in vitro* beta1 rhythm has many implications for cell assemblies (Kopell et al., 2009) that fit well with what is known about beta2 rhythms found *in vivo* in behaving animals. These implications contrast with properties of the PING oscillation. Unlike the latter, if more (tonic) input is fed into some cells that are part of a beta1 assembly, the activation of those cells does not lead to a suppression of the others; rather, they form a separate cell assembly within the old one, firing at additional

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phases. If different streams of input enter different subsets of cells, even at different levels of excitation, these can combine to form a cell assembly within the old beta assembly. Thus, the beta1 context allows cell assemblies to represent simultaneously both past and present, and to do so in ways that allow for multimodal inputs.

Another property of cell assemblies formed in a network displaying beta1 is that the assembly can build up over time: As a sequence of inputs comes and goes, leaving behind groups of cells participating in different beta rhythms, those cells can self-organize into a single assembly. Finally, in the beta1 mode in the rodent S2, the deep and superficial layers have coherent timing. This feature is important for a multimodal structure that interacts with other structures in relation to which the deep and superficial layers of S2 can be either input or output layers.

The ability to not compete comes from the physiology of the beta1 rhythm. In contrast with the gamma rhythm (in which the superficial inhibitory cells are timed by the superficial excitatory rhythms), in beta1, the superficial inhibitory cells are timed mainly by the deep IB cells. The ability to maintain an assembly after the initial signal is gone results from the rebound nature of each part of the concatenation: Once the pattern is set up, it does not need to be activated any further. Since the h-current is modulated by many substances, this rebound is easily controlled. All these properties of the physiology underlying the beta1 rhythm enable superficial excitatory cells to interact in a completely different way than in PING, allowing for flexible manipulation of cell assemblies.

Coordinating Cell Assemblies

So far, we have suggested that the PING version of gamma rhythmicity is effective for producing and protecting cell assemblies, and that the beta1 version of the multimodal areas is an excellent context for manipulating such assemblies after the initial signal is gone. Another aspect of "computing with cell assemblies" is coordinating them. Modeling work from the hippocampus suggests that the theta rhythm can be involved in coordinating cell assemblies that were initially created in the context of gamma rhythms. Specifically, the oriens-lacunosum moleculare (O-LM) cells can cause assemblies of cells firing at gamma frequencies to synchronize (Tort et al., 2007). This can occur even if the cell assemblies are not directly connected with one another via pyramidal cells or fast-firing interneurons. These O-LM cells are known to fire at theta-range frequencies and to participate in theta frequency rhythms *in vitro* even in the absence of excitatory input (Gillies et al., 2002; Rotstein et al., 2005). This observation suggests a different role for the well-known nesting of gamma oscillations within theta rhythms (Chrobak and Buzsaki, 1998; Harris et al., 2003): Rather than providing slots for different cell assemblies in the theta period (Jensen and Lisman, 1996), the gamma system creates cell assemblies that are then coordinated within the theta oscillation. The LTS cells of the neocortex might play a similar role (Gibson et al., 1999).

The interaction of multiple rhythms is an active field of study. *In vivo* studies (Lakatos et al., 2008) have documented the nesting of neocortical rhythms, especially delta, alpha, and theta rhythms in resting animals. A hypothesis from this work is that the slower rhythms provide windows in which the other rhythms are activated. How this might work for coordinating cell assemblies is not yet understood; at a fairly crude level, it could certainly allow multiple inputs to be active simultaneously or to gate the different inputs so that they cannot interact (Lakatos et al., 2007; C. Schroeder chapter herein, Aligning the Brain in a Rhythmic World). The slower rhythms might also act to coordinate cell assemblies that display gamma frequency rhythms, as in the hippocampal example. Another kind of interaction is n:m phase coupling (Palva and Palva, 2007), which would coordinate activity without giving rise to constant phase relationships.

The actual frequencies may also be important for interactions of different subsets of cells. From simpler models of oscillations, it is well known that oscillators with similar frequencies can phase-lock in a 1:1 fashion, and that sufficient differences in frequency make this impossible. For large, network-based oscillations, no theory is yet adequate. However, research seems to suggest that differences in frequencies associated with various mechanisms may indeed be important for determining which pathways are most effective under particular circumstances (Middleton et al., 2008). Differences in frequencies themselves are also thought to be a mechanism for phase precession (Geisler et al., 2007).

We do not adequately understand many properties of interacting network oscillators. However, the more we learn about the physiology of rhythms and the implications of the physiology for networks, the better we will be able to flesh out the ways in which the nervous system uses these properties for cognition.

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