frequency coupling could be used to constrain models of field potential generation. In turn, such models could also be used to elucidate whether there are indeed processes of distinct frequencies that are coupled in the described manner. Such combined model and data-driven investigations will be necessary to ultimately decide whether the reported crossfrequency coupling actually constitutes a phenomenon with biological sources and relevance.

On the whole, these new results draw attention to the arrhythmic components of neural mass activity and highlight that also apparently unspectacular and often ignored signals can reveal surprisingly complex structure.

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Losing Phase

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In this issue of *Neuron*, Remme and colleagues examine the biophysics of synchronization between oscillating dendrites and soma. Their findings suggest that oscillators will quickly phase-lock when weakly coupled. These findings are at odds with assumptions of an influential model of grid cell response generation and have implications for grid cell response mechanisms.

As our moon orbits the Earth, it rotates. Yet on Earth we see only one face of the moon. This happens because the moon happens to rotate by exactly the same amount that it revolves. The matching of angular speeds for rotation and revolution is no coincidence. It is the inexorable result of the periodic movements of the earth and moon combined with the weak gravitational tidal forces coupling them. In the language of the theory of coupled oscillators, the moon's rotation and revolution have converged to the stable phase-locked solution.

In this issue of *Neuron*, Remme et al. (2010) use the theory of weakly coupled oscillators to provide a compelling analysis of the biophysical viability of an influential model of grid cell response generation. Rats and mice (Fyhn et al., 2008 and references therein) have grid cells, and there is good evidence for their presence in humans (Doeller et al., 2010). A single grid cell responds as a function of animal location in two-dimensional (2D) space, with a firing peak at every vertex of a (virtual) regular triangular lattice that covers the plane. The spatial period of the grid cell response is independent of animal speed.

Models of grid cell activity fall into two main classes, both predicated on the hypothesis that position-coded grid cell responses are obtained using animal-velocity cues. Aside from this shared hypothesis, the model classes are disparate in their assumptions and predictions, with each class explaining largely complementary subsets of grid cell properties. One model class assumes that strong network-level recurrent connectivity unleashes a spontaneous patterning of the neural population response (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burak and Fiete, 2009, and references therein). These population responses translate into spatially periodic responses of single neurons. The other model class assumes that interfering temporal oscillations set up a beat wave that can be mapped onto space to produce spatially periodic grid responses (Burgess et al., 2007; Hasselmo, 2008).

Remme and colleagues analyze an exemplar of the temporal interference (TI) models, based on voltage oscillations within a single neuron (Burgess et al., 2007). The model may be summarized as follows: if the soma oscillates at a fixed temporal frequency, and a dendrite

oscillates at a slightly different frequency that increases linearly with the running speed of the animal, then the summed response of the soma and dendrite, when plotted as a function of animal location as the animal runs in a straight line (1D), is periodic and invariant to running speed (Figure 1, top right). The generalization to 2D and to a triangular lattice pattern in space comes from assuming three independently oscillating dendritic branches, modulated in frequency by the component of the animal's velocity along multiples of 120°, respectively. The output of the three branches, when summed, produces a regular triangular lattice pattern characteristic of grid cells. The summation is assumed to occur at the soma, and the dendrites are assumed to be independent intrinsic oscillators whose frequency is determined solely by the external velocity input. The latter assumption is the focus of the study by Remme and colleagues.

In addition to reproducing the spatial aspects of a grid cell's response, the TI models generate for "free" (as an essential consequence) the phenomenon of phase precession, seen in grid cells of entorhinal layer II (but not layer III) (Fyhn et al., 2008). TI models additionally predict that grid cells with a larger spatial period must display lower temporal oscillation frequencies. Experiments in the dorsolateral band of the entorhinal cortex showed that the intrinsic temporal response frequency of neurons increases systematically toward the ventral end (Giocomo and Hasselmo, 2008; Jeewajee et al., 2008), in concert with the observed increase in spatial period of grid cells and with the prediction of the subthreshold voltage version of the TI models. For these reasons, the subthreshold TI model has fueled experimental study and initiated a nascent but growing understanding of the cellular determinants of grid cell response.

However, Remme and colleagues show that the subthreshold TI model's assumptions cannot easily be reconciled with neural biophysics. When two oscillators with similar intrinsic frequencies are weakly coupled, they will become phase-locked, as observed by Christiann Huygens for two pendulum clocks hung from the same wooden beam (Figure 1, bottom left) and noted in his 1665 correspondence to the Royal Society. The universality of the dynamics of weakly coupled oscillators predicts phase-locking (Pikovsky et al., 2002), whether the oscillators in question are gravitational bodies, pendula, chemical reactions, or as shown previously by Remme and colleagues, distant dendritic compartments interacting through the cell membrane (Remme et al., 2009). (If the coupling between oscillators is strong, other interesting phenomena such as "oscillator death" and chaos can occur, but these effects are not considered in the present work because the dendritic interactions are estimated to be in the weak coupling regime.) Therefore, the first conclusion of Remme and colleagues is that is not possible for a grid cell to indefinitely maintain the frequency and phase differences between dendritic compartments required for the perpetual generation of grid responses.

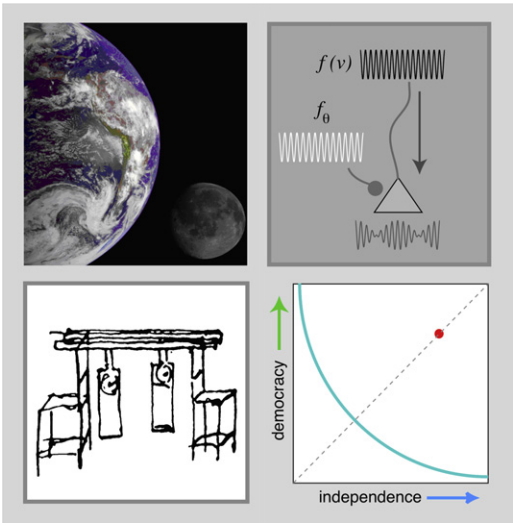

Figure 1. Oscillators and Grid Cells

Top left: the moon shows only one face to Earth-bound observes as it revolves around the Earth. Top right: schematic of the 1D temporal interference model of grid cell response. The soma receives one constant-frequency input from inhibitory interneurons, which it sums with the variable-frequency input of its oscillating dendrite. The amplitude-modulated beat wave, when thresholded, produces 1D grid-like patterns. Bottom left: Huygens' drawing of two pendulum oscillators hung from a beam. The oscillators lock phase through "barely perceptible" motions of the beam. Bottom right (cyan): schematic trade-off curve between greater dendritic independence versus greater influence on the soma (democracy). Increasing membrane leak conductance, dendritic length, or the strength of restorative conductances (e.g., I_h), or decreasing dendritic diameter, produces rightward movement on the trade-off curves (increasing independence but decreasing democracy). The grid cell model of the top right panel assumes conditions far off the biophysical trade-off curves (schematic, red dot). Top left panel is NASA image #PIA00342 from the spacecraft Galileo (1990). Bottom left panel is from Pikovsky et al., 2002.

The ultimate stability of only the phase-locked solution need not exclude the possibility that dendrites may transiently remain independent, for long enough to retain their position-coded phases and produce grid patterns over the 10–20 min during which grid patterns are recorded. The more weakly coupled a pair of oscillators, the more slowly the phase-locked solution is reached. For instance, the same tidal forces that drove the moon's rotation and revolution into phase-locked states are also slowing the Earth's rotation until it phase-locks with the moon. Eventually, the moon will also only see one face of the Earth. Nevertheless, because of the moon's relatively small gravitational effect on the earth, the Earth is slow to phase-lock and still rotates out of step with the moon.

Addressing the question of timescale for phase-locking between dendritic compartments is the central focus of the present work by Remme and colleagues. They use both theoretical and numerical analyses to arrive at quantitative, well-parameterized results that can be grounded in experimental data on membrane properties, synaptic currents, and cell morphology. The basic setup of their analytical model is a pair of dendritic compartments modeled as intrinsic oscillators, coupled by a cable equation. Each dendritic oscillator's phase resetting curve (PRC) defines the change in the phase of the oscillator induced by an infinitesimal input, as a function of the oscillator's present phase. Inputs to the dendrite affect its phase through its PRC. In this model, synaptic velocity inputs change the phase of the ongoing dendritic oscillation, and thus can also alter its instantaneous frequency. Similarly, the state of the other

dendrite also affects dendritic phase through the voltage of the cable that couples them.

In a theoretical analysis of the transient dynamics of this coupled oscillator system, Remme and colleagues identify a fundamental trade-off between ''independence'' and ''democracy'' in dendritic computation (Figure 1, bottom right). If the dendrites strongly influence somatic voltage (democracy), as required for generating the beat wave in the TI model, then by the bidirectionality of electrical coupling, the soma will also affect the dendritic oscillation (loss of independence), degrading the velocity-defined phase information about position contained in the dendrite. In other words, altering dendritic properties to increase independence comes at the cost of a decrease in the influence of (1) the dendrite on the soma (which translates into a decrease of the amplitude of the beat wave) and of (2) synaptic inputs onto the dendrite.

Remme et al. next numerically simulate the voltage dynamics in a morphologically correct spiny stellate cell with active and passive conductances. They show that different parameter combinations sample different points on a set of independence-democracy trade-off curves (Figure 1, bottom right). None of the parameters in their model, varied over biophysically reasonable values, enables the coexistence of sufficiently high levels of democracy and independence to generate spatially periodic grid responses.

Is there a way to reconcile the conflict between the biophysics of neural oscillators and the requirements of the subthrehsold TI model? If the oscillations in the dendritic compartment were produced by oscillatory synaptic input, which unidirectionally drives neural voltage without being affected in return by postsynaptic voltage, it might be possible to realize a regime of strong dendritic influence on the soma and independent dendritic phase. Such alterations call for network mechanisms or the existence of separate cells with temporally periodic outputs whose frequency or phases are modulated by animal speed. Other TI models, including one based on the interference of regular spike trains from persistent spiking neurons of the entorhinal cortex (Hasselmo, 2008), are built on some of these alternative assumptions and generate similar predictions. Unfortunately, all forms of TI models are subject to another biophysical feasibility issue (raised in Welinder et al., 2008 and explored in Zilli et al., 2009), again related to the assumption that spatial information can be faithfully represented in the phase of a temporal oscillation over extended periods of time. Single biological oscillators are typically noisy. The theta peak in the local field potential spectrum is broad, signifying a variable oscillation period and phase loss. Membrane potential oscillations in single entorhinal cells are similarly variable: over fewer than 10 cycles, information about the initial phase is lost (analyzed in Welinder et al., 2008). Even persistent spiking neurons of the entorhinal cortex, despite their low interspike interval variance, would experience loss of phase information at a rate too high for generating grid responses without assuming network-level contributions to grid activity beyond the interference of spikes from cell triplets (Zilli et al., 2009).

At this point, we may be left wondering, ''What are we to conclude about the mechanisms underlying grid cell responses? And with these biophysical caveats on TI models, why are their predictions so successful?''

Like the TI models, recurrent neural network models of grid cell response based on continuous attractor dynamics use velocity inputs to produce periodic grid-like responses. In addition, they necessarily generate groups of cells with identical periods and predict that cells with the same spatial period must have identical orientations but all possible spatial phases, as found in experiments. Cells with combined velocity and grid tuning are another natural byproduct and prediction of the network models (Fuhs and Touretzky, 2006), and their existence was verified by experiment (Sargolini et al., 2006). The models also have some robustness to neural noise in the computation of position-coded phase from velocity over minutes (Burak and Fiete, 2009). For these reasons, recurrent network dynamics remain a viable model for the generation of spatially periodic grid responses.

However, present recurrent network models do not include mechanisms for phase precession. At the same time, over the short durations of a few theta cycles on which phase precession occurs, the biophysical forces that ultimately lead to phase-locking have relatively little effect on soma-dendritic dynamics and are unimportant.

Combining these observations into a composite model in which temporal oscillations and recurrent dynamics play separable roles in explaining grid cell responses, we may provocatively imagine the following division of labor: in the adult animal, continuous attractor network dynamics are necessary and sufficient for generating spatially periodic grid responses, while multiple temporal oscillators are essential for determining temporal aspects of spiking responses, including phase precession. If a similar composite model were a true reflection of the biology, this would explain the predictive successes of both classes of models. A prediction of this specific composite model, with separable roles for temporal oscillations and recurrent connections, would be that spatially periodic responses should be present even in the absence of temporal oscillations. A second prediction is that phase precession should be evident in the presence of intact feedforward input, bringing external sensory cues that supply the system with information about animal location, even after local recurrent feedback in the entorhinal cortex is disrupted.

The ultimate tests of all such ideas and models must come via experimentation. But the work of Remme and colleagues beautifully illustrates how theoretical considerations and numerical computation can unearth basic biophysical constraints, as well as shrink the field of hypotheses into a set that can more manageably be addressed by experiments.

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Listening to the Crowd: Neuronal Ensembles Rule

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In this issue of *Neuron*, Durstewitz and colleagues show that neuronal populations in the medial prefrontal cortex (mPFC) of rats reflect abrupt changes in behavioral strategy as animals learn to act according to new rules in a rule-switching task.

In animal learning experiments, changes in performance are often seen as a gradual process, where new associations or rules are learned progressively over time by trial and error. However, humans often report specific moments of sudden insight, "a-ha!" moments, something that has long fascinated psychologists and others. Indeed, on closer examination, animal studies also reveal abrupt changes in performance, where learning appears to occur over one or just a few trials (Gallistel et al., 2004). It has been suggested that this phenomenon is actually quite common; the reason slow changes are often reported may be simply that performance is being estimated by averaging across trials and animals. This averaging inevitably smoothes out the true learning curves of individual animals. By applying appropriate statistical measures that provide a more sensitive measure of changes in a time series, abrupt changes in performance can sometimes be revealed (Gallistel et al., 2004; Suzuki and Brown, 2005).

While the fact of abrupt learning has gained acceptance as a behavioral phenomenon, the neural substrates underlying such changes remain quite mysterious. Although some forms of synaptic plasticity can be induced in just a short period of high frequency stimulation, most theoretical models, such as reinforcement learning, usually rely on slow and gradual changes in synaptic connections to implement learning (Dayan and Abbott, 2001), suggesting that insight learning depends on features of neural circuits that are not accounted for in conventional models. A key step toward unraveling this conundrum would be to monitor the changes in circuit activity as abrupt learning takes place.

In the current issue of *Neuron*, Durstewitz and coworkers (2010) take a step in this direction, using state-of-the-art statistical analysis along with multielectrode recordings in rats performing a rule-learning task to show a correlation between rapid switches in behavioral performance and rapid switches in medial prefrontal cortex (mPFC) ensemble activity.

Durstewitz and colleagues (2010) trained rats on a "rule-switching" task (Figure 1A). In this task, first the subject must follow a "visual" rule in which the light above a left or right lever signals where reward is available. Once good performance is achieved, the rule is switched to a "spatial" rule: now reward is delivered at one side only, independent of which light is on. In rats, this task is known to depend on an intact mPFC (Floresco et al., 2009) and is considered to be an analog of the Wisconsin card-sorting test, a task used to study response flexibility in humans. Rats acquired the new rule rapidly, with performance increasing abruptly in a few trials, as shown using change point analysis, consistent with the idea that animals go through an "a-ha!" moment when evidence is sufficient to change response rules.

To investigate the neural mechanisms that underlie abrupt rule switches, the authors recorded the activity of up to 16 mPFC neurons simultaneously during the performance of the rule-switching task. The neuronal correlates of associative learning have been studied previously at the single neuron level in several tasks and brain areas, particularly in nonhuman primates (Suzuki, 2008). In these studies, the firing of single neurons (e.g., Chen and Wise, 1996; Zach et al., 2008) or