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Space-Time Dynamics of Membrane Currents Evolve to Shape Excitation, Spiking, and Inhibition in the Cortex at Small and Large Scales

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In the cerebral cortex, membrane currents, i.e., action potentials and other membrane currents, express many forms of space-time dynamics. In the spontaneous asynchronous irregular state, their space-time dynamics are local non-propagating fluctuations and sparse spiking appearing at unpredictable positions. After transition to active spiking states, larger structured zones with active spiking neurons appear, propagating through the cortical network, driving it into various forms of widespread excitation, and engaging the network from microscopic scales to whole cortical areas. At each engaged cortical site, the amount of excitation in the network, after a delay, becomes matched by an equal amount of space-time fine-tuned inhibition that might be instrumental in driving the dynamics toward perception and action.

Neurons causally affect their target neurons by sending action potentials (spikes) through their axons, thereby altering the membrane currents (MCs) of their target neurons. Conversely, exposed to sufficiently strong excitatory MCs, a neuron emits a strong and fast MC, an action potential or spike. These two causal relations form the basic machinery of the brain. The purpose of this communication is to point to various forms of space-time dynamics (STDs) of MCs creating excitation, inhibition, and spiking from fine to large scales in the brain. An additional goal is to examine how particular evolutions of these STDs relate to perception and preparation for action. In accordance with the purpose of this series, gaps in knowledge will be filled by speculations, indicated by an (s) following such statements. If the speculation can be tested experimentally, either by current or future methods, a (t) is added; for example, (s,t) or (s,t future).

What Is Meant by STDs of MCs

The currents passing through the membranes of neurons are carried by the ions Na^+, Ca^{2+}, K^+, and Cl^-. Thus, the total current passing through a local membrane is

$$dV_m(t)/dt = -1/C_m[g_{Na^+}(V_m(t)\text{-}E_{Na+}) + g_{Ca^{2+}}(V_m(t)\text{-}E_{Ca^{2+}}) + g_{Cl^-}(V_m(t)\text{-}E_{Cl^-}) + g_{K^+}(V_m(t)\text{-}E_{k^+})], \quad \text{(Equation 1)}$$

in which C_m is the specific capacitance of these membranes, E is the reversal potential, and g the conductance. The measurement of the time derivative of the membrane potential, $dV_m(t)/dt\ C_m$, at the local membrane of a certain neuron is equal to the sum of the MCs.

MCs are action potentials (spikes) and sub-threshold MCs. MCs are properties of single neurons. However, all neurons are working in a network. STDs in the cerebral cortex are the progression of MC changes and spikes in the space made up of the cortical network of neurons. The cortical network of neurons is the synaptic connected neurons with their cell bodies in the cerebral cortex.

The ultimate explanation of how the cerebral cortex works is mathematical, some might say. As an alternative to describing the STDs in cortical anatomical space, one can use a dynamical systems approach and describe the STD evolution in (abstract mathematical) state space. Both forms of descriptions are relevant. A few concepts are necessary for understanding the STD-MC mechanisms. Network spiking threshold and active spiking are defined in state space (Box 1). Active spiking zones, tight balance, delayed balance, net excitation, and net inhibition are defined in cortical anatomical space.

Network Organization

In the cerebral cortex network, the elements of the neurons are packed closely together, like the elements of a physically compressed car for recycling. Although it is uncertain whether it is rational, all experimental findings relevant for STD-MC stem from the four dimensions made up of time and the compressed mesh of axons, dendrites, cell bodies of neurons, and glia. However, despite the fact that the neuron cell bodies of excitatory and inhibitory neurons are strongly intermingled, they all have fixed, discernable three-dimensional positions marking the origins of the action potentials in their initial axon segment. The cortical network spans from a single synapse (~1 μm^3; Fiala and Harris, 1999) to the whole connected network covering the two hemispheres (~500 cm^3; Pakkenberg and Gundersen, 1997), i.e., more than 14 orders of magnitude. The spikes are located in the single neurons. To create STDs in the network, spikes must propagate through axons and make synaptic changes of MCs in the dendrites and cell bodies of the target neurons. The STD-MC could, in principle, propagate to engage the network from its finest to its largest scale. During the evolution of perception and preparation for action, the STD-MC does

Box 1. Non-spiking, Spontaneous, and Active Spiking States

Excitatory and inhibitory neurons can be in three different states: the non-spiking state, the spontaneous spiking state, and the active spiking state (Hubel and Wiesel, 1959; Huys et al., 2016; Forsberg et al., 2016; Zerlaut and Destexhe, 2017). Single neurons have a spiking threshold: below the threshold, they do not spike; above the threshold, they spike. The dynamical properties of the single neuron determine its spiking threshold. Mathematically, this threshold is a boundary (separatrix) in multidimensional state space (Izhikevich, 2007). This single-neuron spiking threshold is a property of the single neuron and separates its non-spiking state from its spiking states. Some inhibitory and excitatory neurons spike spontaneously. The tight balance between excitatory and inhibitory currents makes the spontaneous spiking chaotic-like and slowly evolving in state space (Huys et al., 2016; Forsberg et al., 2016) (Movie S1). The spontaneous spiking state is a stable state with one fixed-point attractor (Huys et al., 2016). In this state space, there is a separatrix (threshold) at some distance from the fixed point, preventing spontaneous spiking from propagating in the network (Figure 1C) (Huys et al., 2016). This separatrix is a property of the network and separates spontaneous ongoing spiking states from the active spiking states, occurring, for example, in response to sensory stimuli (Huys et al., 2016; Forsberg et al., 2016) (Figure1C). If a perturbation is sufficiently large, the spiking will cross this network spiking threshold and become active spiking (Figure 1C; Movie S1). Active spiking explores state space outside the network spiking threshold (Huys et al., 2016; Forsberg et al., 2016) (Figure 1C; Movie S1).

spread to the mesoscopic scale (10^6 μm^3) and to macroscopic scales (10^9 μm^3 and larger), showing interactions between cortical areas. The explanations of the evolutions of STD-MC across these scales and their relevance for perception and planning of action take up the main part of this paper.

The cortical network can be divided into different cortical areas. A cortical area is usually defined by its unique set of connections to other cortical areas.

The long-range axon connections between neurons in different cortical areas are excitatory (Ottersen and Storm-Mathisen, 1986). Figure 1A shows the gross connections of lower visual areas, parietal areas, inferior temporal areas, and prefrontal areas. One object appearing in the visual field evokes spiking in one zone in one cortical area (retinotopy). If five objects appear in five different positions in the visual field, they will evoke active spiking in five zones in an early visual area. Higher sensory areas have another functional topology; here, one object evokes active spiking in n zones (Figure 1A). A prefrontal area may have active spiking in m zones (Figure 1A).

Network Dynamics In Vivo

The Spontaneous Irregular State

Just as the single neuron influences the network through its spikes, the network dynamics influence the single neurons. When the network apparently is not driven by external stimuli or driven by autonomous spiking from other sites in the cortex, the MCs are asynchronous and irregularly fluctuating; the balance between excitation and inhibition is tight; and the spiking is slow and irregular (chaotic), and many neurons are not spiking (Table 1; Box 1; Rudolph et al., 2007; Huys et al., 2016; Forsberg et al., 2016). In this spontaneous state, in lightly anesthetized and awake animals, some inhibitory neurons spike spontaneously and prevent the few occasionally spiking excitatory neurons from spiking too much (Rudolph et al., 2007; Zerlaut and Destexhe, 2017). At the microscopic scale, the network is "balanced," meaning that the excitatory MCs equal inhibitory MCs in the dendrites and cell bodies (van Vreeswijk and Sompolinsky, 1996). Alternatively, one can interpret the balance as a balanced ratio between excitatory and inhibitory conductances (Equation 1). This does not matter too much; the point is that the balance is not instantaneous. If it were, the neurons could not spike to any excitatory input.

The balance is a property of the local network. Local inhibitory neurons help to keep the balance and keep the stability of the spontaneous state. Dynamically spontaneous spiking evolves around a stable fixed-point attractor, meaning that the spiking is limited to the domain in state space bounded by the network spiking threshold. As the spontaneously spiking inhibitory neurons do not adapt (Rudolph et al., 2007; Ardid et al., 2015; Dehghani et al., 2016), they might be the reason for this stable attractor (s,t). From a small spot in the cortex network containing many dendrites and some cell bodies, the net change in MCs, $dV_{TOT}(t)/dt$, is the sum of the single-neuron MCs, $dV_m(t)/dt$. At this scale, the collective fluctuations of the MCs are small and the network is tightly balanced with short-lasting amplitudes in the excitatory and inhibitory direction (Rudolph et al., 2007) (Figure 1B).

Active Spiking States and Delayed Matching of Excitation with Inhibition

To leave the stable spontaneous state and enter the active spiking states, the tight balance in the network must be broken and the spiking must cross the network spiking threshold (Box 1; Figures 1B and 1C; Movie S1). This may happen spontaneously, when the MC fluctuations are large (Forsberg et al., 2016). Normally, however, it happens when fast successions of action potentials from excitatory neurons, caused by sensory transients or active spiking somewhere else in the cortex, break the tight balance of excitation-inhibition (Huys et al., 2016; Forsberg et al., 2016; Roland et al., 2017). When the $dV_{Tot}(t)/dt$ locally goes significantly below baseline, the term "net inhibition" is used; when $dV_{Tot}(t)/dt$ goes significantly above baseline, the term "net excitation" is used.

The transition from spontaneous spiking states to active spiking states (Box 1) and the transition from the tight balance to a delayed balance of excitation-inhibition occur simultaneously (compare Movie S1 and Figure 1C with Figure 1B). The non-adapting spiking inhibitory neurons may compensate excitation up to the network threshold (Huys et al., 2016) (Box 1; Figure 1C). However, when the tight balance is broken, more inhibitory neurons must be recruited to balance the rise of

spiking of the excitatory neurons (Dehghani et al., 2016), which might happen with variable delays (Figures 1B and 1D; Movie S1). In practice, the integrated amount of net excitation will, locally at the fine mesoscopic scale (5×10^6 μm^3), after a delay, be balanced by an equal integrated amount of net inhibition in dendrites (and cell bodies). This happens whether the balance is disrupted by a single episode of net excitation or several net excitations (Roland et al., 2017). Consequently, over time and with varying delays, the net excitations and net inhibitions will match locally. This rule might apply for all cortical areas (s,t) (Figure 1D). The durations of the net excitation and net inhibition episodes may vary from 50 ms in primary sensory areas to more than 1,000 ms during retrieval of memories and preparation for voluntary movements (Matsumura, 1979; Roland et al., 2017) (Figure 1G).

Actively spiking excitatory neurons locally create more actively spiking excitatory and inhibitory neurons to form active spiking zones, presumably as a consequence of local connectivity (Stepanyants et al., 2009) (s,t). Active spiking zones are parts of the network where neurons in active spiking states dominate the production of spikes. The concept of active spiking zones in the cortical network simplifies the explanations of the spiking STDs, but obscures the causal relations between afferent and local spiking. The active spiking zones are dynamic; the number and spatial distribution of the actively spiking neurons change quickly. The zone may extend through all six layers at some locations, but not at other locations. The lateral extend varies considerably in supragranular, granular, and infragranular layers (Harvey et al., 2009; Forsberg et al., 2016). Figure 1A is a heuristic cartoon showing gross connections between areas with active spiking zones. In practice, there might be many actively spiking zones in a one-zone area, and consequently, the actively spiking zones in an n-zone area may be confluent (s,t). In Figure 1A, the layer compositions of the active spiking zones and the fact that active spiking zones are often bilateral are suppressed.

Active spiking neurons create dynamic space-time structures of overall net excitation and overall net inhibition at mesoscopic and macroscopic scales. These large net excitations and net inhibitions help to drive the brain toward perception and planning of behavior (see later). To be dominant at these scales, the excitations and inhibitions must originate mainly from dendrites, as axons have few synapses (located at the terminals) and cell bodies only make minor contributions to membrane surfaces of cortical neurons (Fiala and Harris, 1999). This is consistent with in vivo Ca^{2+} imaging (Grienberger et al., 2015). At the mesoscopic scale, the net excitations and net inhibitions appear coherent with borders sharper than the average dendritic span (Kremkow et al., 2016) (Figure 1E; Movies S2, S3, S4, and S5). At the microscopic scale, they consist of single-membrane segments with inward and outward currents that can be very precise and have shorter delays, despite being part of a large net excitation (see section on Perception).

One can distinguish typical spontaneous irregular spiking from active spiking on their STDs in cortical anatomical space. Spontaneous spiking appears sparsely at unpredictable isolated positions in the network, whereas the active spiking has a space-time structure (active spiking zones) (Lamme, 1995; Roland et al., 2006, 2017). Similarly, typical asynchronous irregular fluctuations of the $dV_{TOT}(t)/dt$ are short lasting and larger ones appear at unpredictable positions in the cortical network in the prestimulus period, whereas the STDs of the evoked net excitations and net inhibitions have a space-time coherent structure in spatially unfiltered data (compare Movies S2, S3, S4, and S5 with Movie S6).

Typically, the active spiking of excitatory neurons increases to a maximum, driving the membrane potential up and exciting the local inhibitory neurons in the active spiking zone (Figures 1B and 1D–1G; Movie S2). When the excitatory drive diminishes, the inhibitory neurons dominate and drive the network dendrites locally for fine details, and overall into a longer lasting mesoscopic and even macroscopic net inhibition. This stabilizes and protects the network from excitation, restricts the current spiking (Roland et al., 2017), quickly drives the network toward perception, and finalizes the preparation for a (voluntary) movement (see later). Inhibition eventually returns the network to the initial spontaneous-activity state (Figures 1C and 1D).

Examples of Intra-area Dynamical Space-Time Structures

Details of the spiking mechanisms leading to these STDs of excitation and inhibition are given in the references in this and the next section.

Space-Time Spreading Net Excitation and Net Inhibition

The actively spiking excitatory neurons in a zone can monosynaptically and polysynaptically (Roland et al., 2017) drive neurons (mainly dendrites) in the surrounding network in the same cortical area into a laterally spreading net excitation, often covering a whole area (10^{10} μm^3) (Movie S2).

The net excitation outside an actively spiking zone has, with small delays, similar temporal dynamics as the STD-MC in the actively spiking zone (Roland et al., 2017). By this, the actively spiking zone, or zones, dominates the sub-threshold STD-MC in its surroundings and engages very large populations of neurons without increasing the dimensionality of the dynamics significantly (Roland et al., 2017), i.e., without increasing the number of neurons doing different spiking and having different MC changes. A new actively spiking input to the area adds excitation to the spreading excitation and thus interacts with the other active spiking zone(s); for example, to produce illusions (Jancke et al., 2004; Ahmed et al., 2008). The spreading net excitation increases the membrane potentials and hence the driving forces of the inhibitory currents between active spiking zones. The spreading net inhibition that inevitably follows covers the same cortical territory (delayed balance), reduces the dimensionality radically, and confines the active spiking to narrow zones in the network (Roland et al., 2017). Thus, by this mechanism relatively few excitatory neurons engage a vast population of neurons. The subsequent inhibition, starting inside the active spiking zones, then inhibits this vast population. This stabilizes the network and makes its response robust.

Moving Active Spiking Zones, Pre-depolarization, and Sweeps

Stimuli moving relative to peripheral sensory receptors cause moving active spiking zones ($\sim 10^9$ μm^3, lower visual areas; Figure 2). The actively spiking neurons spread net excitation in one direction within an area, presumably through horizontal

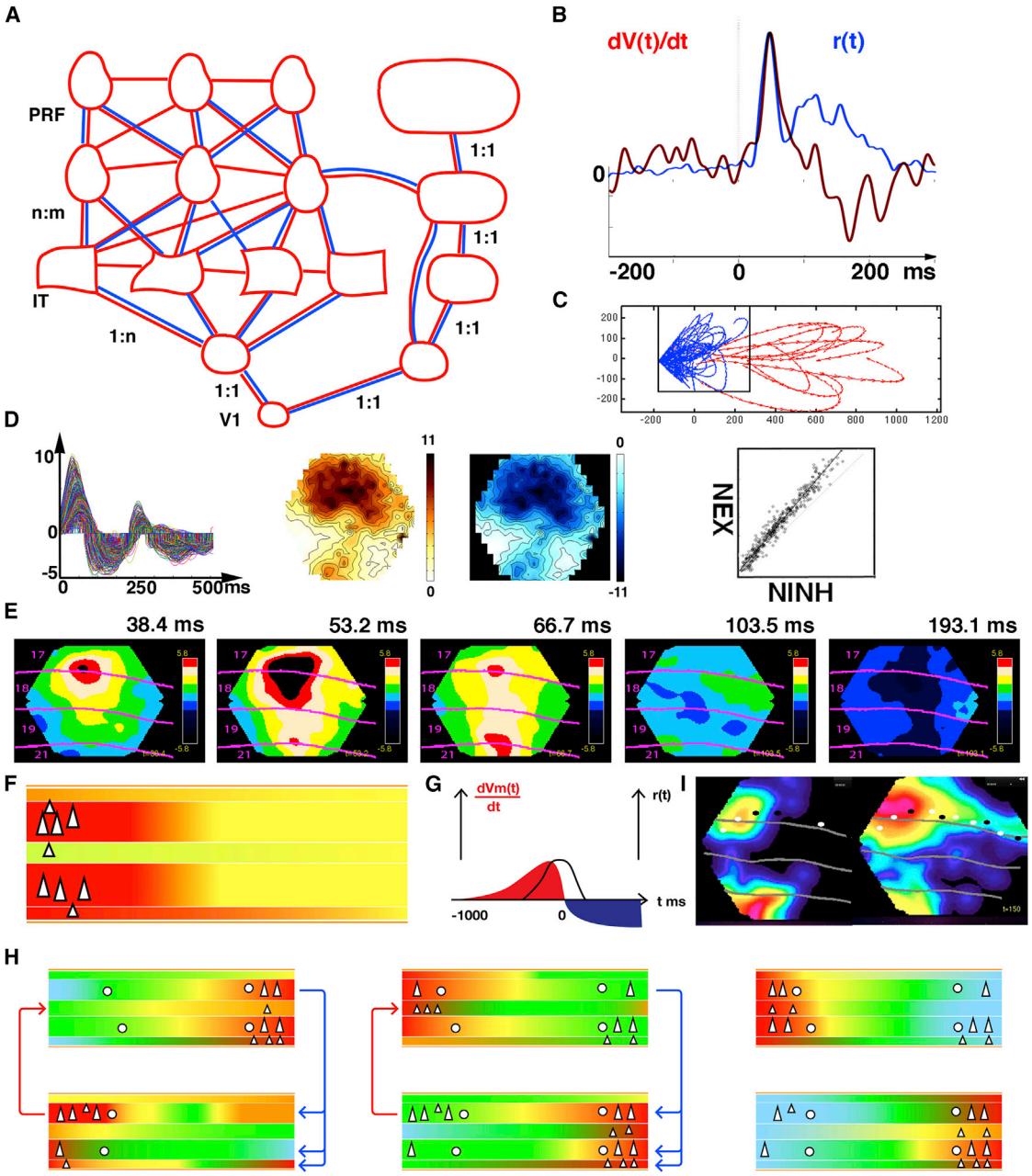

Figure 1. Network Architecture and Basic Dynamics

(A) Cartoon showing the gross connections of active spiking zones in the cortical network of visual and prefrontal areas. Red, bulk of excitatory axons connecting upward; blue, bulk of excitatory axons back-projecting to lower areas (based on Fujita and Fujita, 1996; Pucak et al., 1996; Schroeder et al., 1998; Wang et al., 1998; Rempel-Clower and Barbas, 2000; Borra et al., 2010; Anderson et al., 2011; Markov et al., 2014).

(B) Dark red curve: tight (−200 to 25 ms after stimulus onset) and delayed (25 to 250 ms) balance between network excitation and inhibition. Blue curve: instantaneous spiking rate from the supragranular layers in the same spot of area 17 (modified from Roland et al., 2017).

(C) State-space vectors, ms by ms, of 10 trials of spontaneous ongoing spiking in blue (−200 to 25 ms after stimulus onset) and active spiking vectors in red (25 to 60 ms). Black box: rough estimate of the separatrix (network spiking threshold) (modified from Huys et al., 2016).

(D) Left: statistically significant net excitations and net inhibitions from the colored parts of visual areas 17, 18, 19, and 21 shown in the two middle figures that show the spatial distribution of average net excitation and net inhibition in the 500 ms. Scale values to be multiplied by 10^{-7}. Right: correlation, cortical point by point, of average net excitations (NEX) with average net inhibitions (NINH) in the same animal (modified from Roland et al., 2017).

(E) Net excitation leads to net inhibition. Snapshots of significant $dV_{Tot}(t)/dt$ (net excitations, black, red, beige, and yellow; net inhibitions, blue and dark blue) of five animals to a contrast-defined 2° × 2° square at 0 ms (from movie in Roland, 2010).

(F) Pre-depolarization (Roland, 2010). Actively spiking excitatory neurons in layers 3 and 5–6 by their intra-cortical axons depolarize adjacent cortex. When an external excitation hits the pre-depolarized cortex, the excited neurons easily pass into active spiking.

(legend continued on next page)

Table 1. Dynamic States of the Brain

MCs	Excitation-Inhibition	Spiking States
slow oscillations[a]	bistable[a]	non-spiking
asynchronous irregular[b]	tight balance	spontaneous irregular[b]
evoked excitation and inhibition	dynamic delayed balance	active spiking

[a]Sanchez-Vives et al. (2017)
[b]Zerlaut and Destexhe (2017)

connections in cortical layers 3 and 5 (pre-depolarization, $\sim 5 \times 10^8$ μm^3) (Roland, 2010) (Figure 1F). Pre-depolarization facilitates the transition to active spiking states when a layer 4 or other excitatory input comes (Harvey et al., 2009; Harvey and Roland, 2013). As the directionally spreading pre-depolarization and the laterally spreading net excitation often evolve in the same time window, their STDs often become superimposed (Harvey et al., 2009) (Movie S4). Sweeps are net excitations running across the cortical network from one point to another ($\sim 3 \times 10^9$ μm^3; Slovin et al., 2002). Some sweeps may arise from elongation of an actively spiking zone producing synaptic excitation moving in a certain direction (see STDs of Movement Preparation).

Inter-area Dynamics

Fast-timed active spiking may create active spiking zones throughout a hierarchy of sensory areas (Figure 2) (s,t). Slowly increasing spiking raises the net excitation slowly. Such an increasing pre-depolarization may last long, waiting for an excitatory input from other areas that efficiently starts spiking in the active state (Figure 1G) (see STDs of Movement Preparation).

Back-propagating excitation through axons from higher areas will tend to arrive to targets in lower areas when moderate active spiking has replaced the initial spiking transient, when the membrane potentials are high, and just prior to the switch to net inhibition ($\sim 10^9$–10^{10} μm^3). The back-propagating excitation may drive phase alignment and predictive depolarizations, and aids in correcting asymmetry between areas (Roland et al., 2006, 2017; Ahmed et al., 2008; Harvey et al., 2009; Roland, 2010).

Two areas that are mutually directly connected will tend to establish symmetry in active spiking zones. If one cortical area has an active spiking zone, this zone will soon establish an active spiking zone in its target zone in the other area (Ahmed et al., 2008) (Figure 1H). This mutual excitatory adjustment mechanism may be important for the STDs when perception and planning of movement evolve (s,t).

The predictive depolarization and spiking (Harvey et al., 2009) are an excitation of the network ahead of an active spiking zone in a certain direction to establish a new zone of net excitation and moderate active spiking ($\sim 10^9$ μm^3). The cortical network in between the two zones usually also gets rapidly excited to make one elongated active spiking zone (Figure 1I; Movie S3). In lower sensory areas, the predictive depolarizations are induced by back-propagating excitation from higher areas (Harvey et al., 2009; Harvey and Roland, 2013).

Perception: An Example of Space-Time MC Dynamical Structures Forming Vision

Most vision starts with a sharp transient, when the eyes open, after a saccade, or when something suddenly enters the field of view. Within 120–150 ms, the visual scene is perceived and its objects recognized (Thorpe et al., 1996). Figure 2 illustrates the STD evolution from the transition to active spiking states to the final spreading inhibition producing space-time spiking that after 120 ms is in harmony with a precise interpretation of a rectangular $1^\circ \times 2^\circ$ object moving upward from the peripheral field of view. This evolution mobilizes almost all the space-time structures described in the previous sections.

Moving active spiking zones propagate through visual and prefrontal areas, accompanied by lateral spreading excitation and superimposed directional pre-depolarizations engaging large populations of neurons. Back-propagating excitation produces phase alignment between areas, predictive depolarization, and spiking calibrated to bring the object into focus (Harvey et al., 2009). These automatisms bring the object into focus by a catch-up saccade (s,t) (Figure 2, steps 1–8). The now stationary object image on the retina gives rise to stationary active spiking zones and new lateral spreading excitation in the visual areas. Back-propagating excitations correct shape and size mismatch between areas (s,t) and segment the focused object from its background (Lamme, 1995; Lee, 2003; Gilad et al., 2013; Zurawel et al., 2014). This is done under net inhibition of most dendrites confining the active spiking to narrow retinotopic zones (Roland et al., 2006, 2017) and shape zones (inferior temporal cortex, IT) (s,t) in the network at 120−140 ms (steps 9–18, Figure 2). The inhibitory regime stabilizes the perception until the object disappears (Movie S2). The action potential traffic between the active spiking zones is reduced to the moderate traffic signaling the current scene (Eriksson et al., 2010). Lateral spreading excitation, back-propagating excitation, contour enhancement, figure-background enhancement, and sweeps have also been observed in awake, perceiving monkeys (Slovin et al., 2002; Ayzenshtat et al., 2010; Meirovithz et al., 2010; Gilad et al., 2013; Zurawel et al., 2014).

With the exception of the active spiking, the STD excitations and inhibitions of the cortical network were all in the mesoscopic or even macroscopic scales (see previous sections; Figure 2; Movies S2, S3, S4, and S5). The mesoscopic and macroscopic inhibition, however, does not imply imprecision. The timing and amount of microscopic inhibition of the dendrites and cell bodies confine the spiking of excitatory neurons with high precision to produce fine luminance contrast details of the visual scene (Lamme, 1995; Lee, 2003; Monier et al., 2003; Eriksson et al.,

(G) Slow, smooth increasing excitation also brings the spiking (black curve) over the single-neuron and network spiking thresholds. The subsequent (blue) net inhibition finishes the memory retrieval or movement planning.
(H) Two areas mutually connected by excitatory axons adjust their active spiking rapidly. The triangles are actively spiking excitatory neurons; the circles actively spiking inhibitory neurons. Green and light blue layers are net inhibited; yellow, orange, and red layers are net excited (s,t).
(I) Two snapshots showing the predictive depolarization and spiking (white circles) at 110 and 145 ms after the appearance of a moving bar (Movie S3).

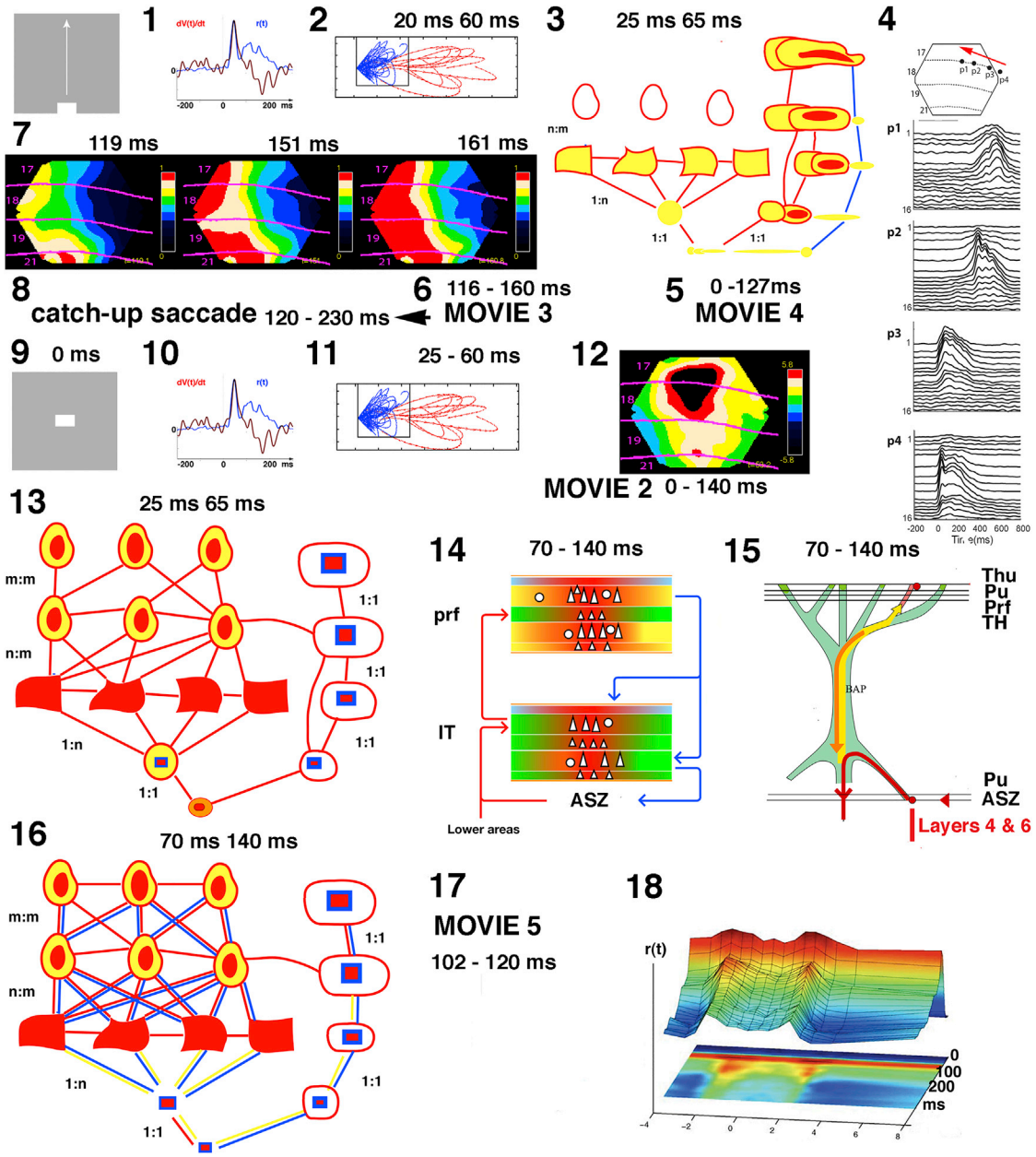

Figure 2. Visual Perception as an Example of Space-Time Mechanics of MCs

The numbers refer to mechanisms partly overlapping in time. Time 0 ms when scene starts. (1) Sharp spike and excitation transients cause (2) active spiking propagating through layers and visual areas, (3) giving rise to active spiking zones moving through all cortical layers (4) and extending ahead of the retinotoppic object position (3). (5) STD-MC spreading excitation, directional pre-depolarization, back-projecting excitation, and spreading net inhibition in Movie S4. (6) Predictive depolarization and spiking in Movie S3 promoting catch-up saccade planning. (7) Back-projecting excitation and phase aligning of membrane potentials in lower visual areas. After saccade (8), the object is in focus (9). New sharp transient driving spontaneous spiking into active spiking across areas (10), (11), and (13) (s,t) and subsequent spreading excitation (12) (Movie S2). (14) Recurrent excitations, within and between areas and between layers, provide dense spiking from Prf (prefrontal cortex), Thu (thalamic unspecific nuclei), Pu (pulvinar), TH (area TH parahippocampal), and ASZ (other active spiking zones in inferior temporal cortex), reaching distal and basal dendrites of inferior temporal lobe pyramidal neurons to provoke back-propagating AP (BAP) and opening of Ca^{2+} channels (15) (s,t). (16) Back-projecting excitations from temporal and parietal visual areas correct for mismatch of size and shape between active spiking zones (s,t), (17) segment the object from its background (Movie S5), and start net inhibition (Movie S2) at 110 ms, suppressing spiking outside the active spiking zone corresponding to the retinotopic location of the object (18) (modified from Lee, 2003) (based on references in sections on Network Dynamics In Vivo and Intra-area and Inter-area Dynamics and Baylis and Driver, 2001; Eriksson et al., 2010; Schroeder et al., 1998; Slovin et al., 2002; Wang et al., 1998).

2008; Ozeki et al., 2009; Harvey and Roland, 2013). Movies S7 and S8 illustrate this for a visual scene in which two objects move to occlude one another.

The local temporal dynamics of spiking and MCs, however, do not distinguish simple visual scenes on a single-trial basis (Forsberg et al., 2016). The STDs of MCs of the network in four

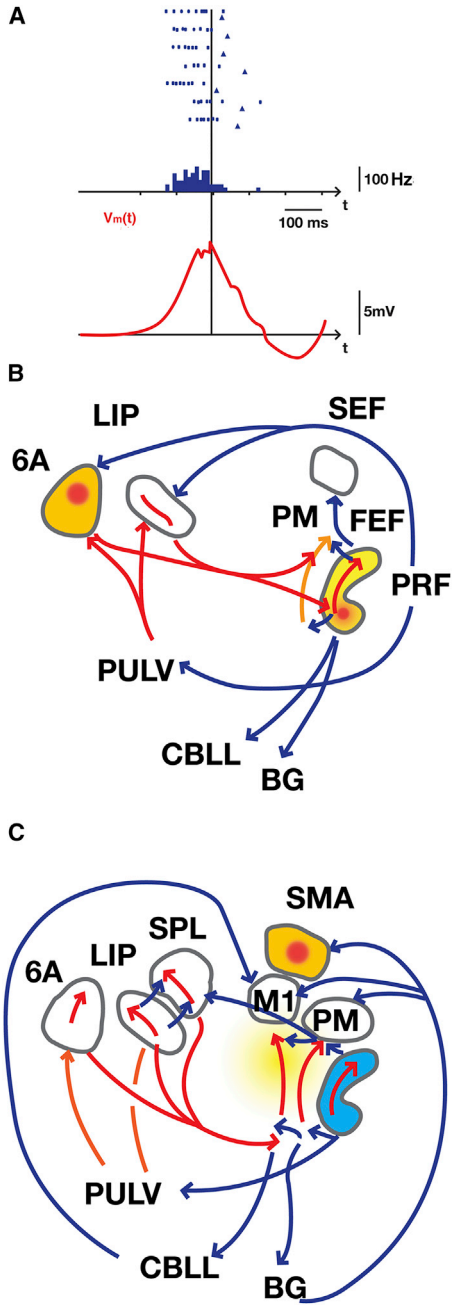

Figure 3. Initiation of Behavior

(A) Intracellular recording of membrane potential (red) and single-trial spiking of a neuron in primary motor cortex (M1). Muscle activity starts at vertical line; movement starts at the triangles (modified from Matsumura, 1979).

(B) Preparation for reaching starts with a saccade. The excitatory sweep specifying the amplitude of the saccade in the FEF is exported to PM (s,t).

(C) A matching sweep is produced by the saccade itself, amplifying the existing sweeps in LIP, SPL, PM, and M1 finger-hand-arm region, starting the reaching after 1,000 ms preparation. Once the sequence of engagement of fingers, hand, and arm propagates to all actively spiking areas and becomes in phase, the reaching starts with fast increase of the spiking of the local inhibitory neurons (Matsumura, 1979; Isomura et al., 2009) (A and C).

6A, area 6A; BG, basal ganglia; CBLL, cerebellum; FEF, frontal eye field; LIP, lateral intraparietal area; M1, primary motor cortex; PM, premotor cortex; PRF, prefrontal cortex; PULV, pulvinar; SEF, supplementary eye field; SMA, supplementary motor area; SPL, superior parietal lobule (based on Fried et al., 2011; Fetz et al., 2000; Matsumura, 1979; Slovin et al., 2002; Gottlieb and Balan, 2010).

retinotopic visual areas, in contrast, reduce to flows on a three-dimensional manifold early after the appearance of the scenes. The flows distinguish simple individual visual scenes after 45 ms and continue to diverge on the manifold beyond 120–150 ms and until the scenes disappear from view (Roland et al., 2017).

But is it possible to reveal the brain's interpretation of the visual surroundings by measuring the STD-MC of the cortex? First, only by following the entire evolution of the STDs in the cortex (Figure 2) would one realize that an upward moving bar was brought into focal vision. Second, even when spiking in an early visual area is retinotopic and correctly reflects the physical contents of the visual scene, back-propagating excitation from higher areas can transform this into an illusion in less than 100 ms (for example, to signal apparent motion of stationary objects quickly flashed at different positions; Ahmed et al., 2008). Third, as shown (Movies S2, S3, S4, and S7), the STD of excitation was at no point retinotopic and was thus not isomorphic with the visual scene. The STD ended in widespread inhibition at the time when perception of the scene is supposed to take place (120–150 ms). So only if the STD-MC of all cortical areas with active spiking is measured simultaneously might there be a chance to reveal the brain's interpretations of visual surroundings (s,t future?).

Initiation of Movements

Like perception, motor actions are not carried out with fixed relations between the surroundings and the animal. Relations between the position of the limbs and objects in the surroundings are not fixed. This implies that the brain usually does not have an exact memory stored of a precedent situation when, for example, the animal plans to reach for an external object. In such situations, the brain must predict the future relationship between object and body parts (s,t).

STDs of Movement Preparation

Cortical motor neurons, during rest in vivo, have a membrane potential that is far from the spiking threshold (about −70 mV) (Matsumura, 1979). Neurons in the primate primary motor cortex are presumably under a stronger inhibitory control than elsewhere in the cortex. They often require synchronous excitation from neighboring neurons to build up excitatory MCs of 100 ms or more, after which they fire and initiate local net inhibition (Matsumura, 1979; Fetz et al., 2000) (Figure 3A). The planning of a voluntary movement often takes more than 1,000 ms (Fried et al., 2011) and may involve an iterative STD-MC-spiking coordination of many populations of neurons (s,t). Thus, the temporal dynamics of movement preparation in motor areas are slow and smooth, as opposed to dynamics driven by fast sensory transients. These factors reduce the likelihood that autonomous spontaneous transitions into active spiking within the motor system start (voluntary) movements (s,t). Overt behavior is more likely initiated outside the motor system, by internal inputs (i.e., thinking) or by sensory inputs (s,t).

Reaching for an interesting object in the surroundings is initiated by a saccade to that object (Gottlieb and Balan, 2010). The saccade causes excitatory sweeps (section on Intra-area Dynamics) mapping the transition from the fixation point to the target in the one-zone areas 6A, lateral intraparietal cortex (LIP), and frontal eye fields (s,t). The idea is that the frontal eye field sweep excites the neighboring premotor cortex to produce a similar excitatory MC sweep, starting the preparation for the reaching as shown in Figures 3B and 3C (s,t). The inhibitory neurons in the primary motor cortex finalize the preparation and start the reaching (Figures 1G and 3A). These sweep STDs have the advantage that the brain can implement reaching without explicit ''information'' of the position of the arm. As far as I can see, this is not in contradiction with experimental results.

Outlook

Perception and initiation of movements (and thoughts) are space-time effects that have causes preceding them. Explanations about how brains work should reveal how STDs in the brains lead to such effects. STDs of MCs, including action potentials, are certainly needed for perception and planning behavior. This report gave some incomplete provisional explanations of how particular perturbations of the spontaneous irregular state lead to active spiking states of neurons starting diverse forms of excitatory STDs related to vision and preparation for movement in carnivore and primate brains. However, causal relations between afferent active spiking sources and local active spiking in the cortical network cannot yet be revealed. Similarly, the STDs of active spiking and STDs of excitation and inhibition in large parts of the cortical network, e.g., higher-order visual and prefrontal areas, have not yet been revealed.

The cortical network transcends scales from single synapses to cortical areas. The STDs start with synaptic excitation and active spiking spreading through the network. The active spiking neurons invade large populations of neurons in spontaneous state with the excitatory temporal dynamics of the active spiking zones, though without increasing the dimensionality too much in the now-engaged cortex. The result is diverse forms of large mesoscopic and macroscopic excitations. Superposition and the combined and sequential action of these net excitations engage populations of neurons as large as possible, taking over the dynamics of the network at the largest scale. These large net excitations sooner or later inevitably lead to spatially matching inhibition that engages most of the dendrites, radically reduces dimensionality, and holds these large populations in the current task, while at the same time confining the spiking to express fine details in the evolving percept or start of behavior. This implies that perception and start of movements take place under inhibitory regime. The temporal dynamics of spiking or MCs of single neurons or local populations tell the changes in excitability that distinguish the spontaneous states from the active states, but are unlikely to distinguish all different percepts, thoughts, and voluntary movements, which only the STDs of the entire network can distinguish.

The advantage of the spike and STD-MC hypothesis is that it is independent of assumptions of spiking of particular neurons and particular subpopulations of neurons. In contrast, the creation of the percept, thought, or planning of the behavior is done by all actively spiking neurons. Similarly, no assumptions are needed about specific relations between items or features in the surroundings and spiking patterns, spiking codes, spiking statistics, synchronicity, noise, internal models, etc. in the brain. The spike and STD-MC both explain how veridical visual perception and visual illusions appear by combinations of the mechanisms and obey time constraints for recognition, perception, and planning of behavior. Finally, most of the proposed mechanisms can be tested experimentally with current methods.

SUPPLEMENTAL INFORMATION

Supplemental Information includes eight movies and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2017.04.038.

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